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(54) Title: T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME (57) Abstract <p>The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.</p>		

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T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

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TECHNICAL FIELD OF THE INVENTION

The present invention relates to cloned T-type calcium channels.

BACKGROUND OF THE INVENTION

Biological membranes are themselves generally impermeable to ionic species. Thus, ions enter cells through regulated pores formed from membrane-associated proteins. Most of these regulated pores are voltage-dependent and are thus able to transduce changes in the transmembrane potential into ion flux. Voltage-gated ion channels form a "superfamily" of related proteins (cf. Jan et al., *Nature*, 345, 672 (1990)). Peculiar to this genus is a high degree of conservation in molecular structure. Generally, voltage-gated channels are membrane bound glycosylated proteins formed of many subunits. Large α subunits form a pore in the membrane that is selective for a given ionic species. Each α subunit contains four domains (I, II, III, and IV). Each channel domain has six putative transmembrane helical segments (S_1 - S_6). In general, the segments within each domain are similar but not identical. Aside from overall structural conservation, certain charged residues within the domains are highly conserved among voltage-gated ion channels (Jan et al., *supra*; Stühmer et al., *Nature*, 339, 597-603 (1989)).

Differences in charged residues between groups of voltage-gated ion channels confer properties unique to each subgroup, such as ion selectivity. For example, most voltage gated ion channels are selective for either sodium, potassium or calcium. Known calcium channels require a ring of negative charge provided by glutamate residues found at similar locations in each of the domains (Yang et al., *Nature*, 366, 158-61 (1993)).

Voltage-gated channels are often classified on the basis of their electrophysiology. The resting membrane potential of most animal cells is between about -70 mV and -80 mV. When the membrane becomes depolarized (moved towards 0 mV), various membrane channels become activated (they are said to

“open”). Thus, one basis for classifying membrane channels is the membrane potential necessary to activate (or “gate”) them (voltage dependency). For example, “T-type” calcium channels are activated at a lower voltage than L- or N-type channels (Nowycky et al., *Nature*, 316, 440-43 (1985)). Other physiological properties are the activation kinetics, inactivation kinetics, tail current (deactivation kinetics), and single channel conductance. Thus, in comparison to other calcium currents, T-type calcium current is characteristically short (Chen et al., *J. Gen. Physiol.*, 96, 603-30 (1990)), and it exhibits characteristically slow activation kinetics near threshold, fast inactivation kinetics, and slow tail current (Randall et al., *Neuropharmacol.*, 63, 879-93 (1997); Carbone et al., *Nature*, 310, 501-02 (1984); Nilius et al., *Nature*, 316, 443-46 (1985)).

Calcium currents have been implicated in many neurological and muscular functions. For example, T-type calcium current is associated with cardiac pacemaker activity, pain transmission in the central nervous system, and in other physiological functions. Defects in T-type calcium current have been implicated in cardiac arrhythmia, hypertension, and epilepsy. Given their potential clinical value, the pharmacological properties of calcium channels have been the subject of extensive study. Most such studies have involved L-type channels because, unlike T-type channels, L-type calcium channels are readily purified from cell extracts. For example, L-type calcium channels have been purified using dihydropyridine drugs (e.g., nifedipine) which can bind with sufficiently high affinity to serve as a ligand for purifying L-type calcium channels. Such purified and cloned L-type calcium channels have been used to develop assays for drugs affecting L-type calcium channels (see, e.g., U.S. Patents 5,429,921 and 5,386,025).

While many electrophysiological characteristics of T-type calcium currents are known, the lack of isolated T-type channels has stalled research into the pharmacology and biophysics underlying the T-type calcium current, at least in comparison with other calcium channels. Indeed, while it is generally assumed that voltage-sensitive ion channels are responsible for the current, no such channel protein, nor any nucleic acid encoding such a protein, has been isolated. In view of the foregoing problems, there exists a need for an isolated T-type calcium channel and a nucleic acid encoding a T-type calcium channel.

BRIEF SUMMARY OF THE INVENTION

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or

substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

The present invention is useful for exploring the electrophysiology and pharmacology of the T-type calcium current. Such knowledge can lead to the development of drugs for potentiating or attenuating T-type calcium channels. Thus, the present invention provides an assay for identifying potential drugs affecting T-type calcium channels by exposing cells expressing a T-type calcium channel to a putative drug and then measuring the calcium flux in response to a change in membrane potential. The identification of drugs affecting T-type calcium channels will facilitate even greater understanding of the biophysics of these proteins. Furthermore, some such drugs could have potential clinical applications.

The invention can best be understood with reference to the accompanying drawings and in the following detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1E compare the complete amino acid sequences of three types of T-type calcium channels ($\alpha 1G$ (or Ca_vT.1), $\alpha 1H$ (or Ca_vT.2), and $\alpha 1I$ (or Ca_vT.3)), indicating conserved functional domains.

Figures 2A-2D are graphic representations of the current-voltage relationships of three cloned T-type calcium channels (Figures 2A, 2B, and 2C) and a cloned R-type calcium channel (Figure 2D).

Figure 3A is a graphic representation of the average current-voltage curve for cloned T-type calcium channels ($\alpha 1G$, triangles, $\alpha 1H$, inverted triangles, $\alpha 1I$, circles), and a cloned R-type calcium channel (filled squares). Figure 3B compares the normalized conductance of a cloned T-type calcium channel at three different concentrations of BaCl₂.

Figure 4 depicts average kinetics of the tail current as a function of repolarization potential for $\alpha 1G$ (triangles), $\alpha 1H$ (inverted triangles), $\alpha 1I$ (circles), and a cloned R-type calcium channel (filled squares).

Figures 5A and 5B graphically present data concerning the use of a cloned T-type calcium channel to detect drugs affecting the channel. Figure 6A depicts the effect of 100 μM on current-voltage relationships with a single dosage of mibefradil. Figure 6B illustrates the effect on T-type channel conductance of various doses of mibefradil.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α

subunit. The nucleic acid can be of any type, and it can include other elements aside from a sequence encoding a T-type calcium channel domain or domains. For example, where the nucleic acid comprises RNA, it can also include regulatory sequences suitable to permit translation of the RNA. Thus, an RNA nucleic acid of the present invention preferably has at least one ribosome entry site, and preferably has a polyadenosine tail for stabilizing the RNA in the cellular environment.

Similarly, DNA nucleic acids of the present invention can have regulatory elements for promoting the transcription of sequence encoding the T-type calcium channel into an RNA such as that described above. For example, a DNA nucleic acid of the present invention can have a promoter and/or an enhancer sequence. While the nucleic acid can be any type of nucleic acid, the nucleic acid preferably comprises a cDNA. A cDNA nucleic acid is preferred over other nucleic acids to permit the nucleic acid to be readily cloned, sequenced, and expressed in a wide variety of cells.

The choice of promoter and/or an enhancer will largely depend on the milieu in which the nucleic acid is to be expressed. Thus, for expression in bacterial cells, the regulatory elements are bacterial promoters. Similarly, for expression in mammalian cells, the regulatory elements are able to effect expression in mammalian cells. While many such regulatory elements are known in the art, examples include prokaryotic promoters and viral promoters (e.g., retroviral ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit β -globin regulatory elements), constitutively active promoters (e.g., the β -actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters (e.g., those active in epidermal tissue, dermal tissue, tissue of the digestive organs (e.g., cells of the esophagus, stomach, intestines, colon, etc., or their related glands), smooth muscles, such as vascular smooth muscles, cardiac muscles, skeletal muscles, lung tissue, hepatocytes, lymphocytes, endothelial cells, sclerocytes, kidney cells, glandular cells (e.g., those in the thymus, ovaries, testicles, pancreas, adrenals, pituitary, etc.), tumor cells, cells in connective tissue, cells in the central nervous system (e.g., neurons, neuralgia, etc.), cells in the peripheral nervous system, and other cells of interest).

The isolated or substantially purified nucleic acid of the present invention encodes all or part of a T-type calcium channel α subunit. As used herein, a "calcium channel" includes a protein structure for facilitating the flux of calcium ions across a biological membrane into which the calcium channel is inserted. As used herein, a "T-type channel" is a type of voltage-gated ion channel that facilitates the flux of ions

when the membrane potential of a biological membrane into which it is inserted experiences a slight depolarization. Thus, a T-type calcium channel can begin to gate from about -60 mV to about -30 mV (i.e., about -45 mV to about -35 mV) in about 10 mM Ba^{2+} . Additionally, T-type channels of the present invention exhibit a slow
5 deactivation (tail current) following depolarization. Thus, a T-type calcium channel can exhibit a tail current that decays exponentially with a tau value from about 1 ms to about 10 ms (e.g., from about 4 ms to about 7 ms, such as about 6 ms) following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a Ba^{2+} concentration of from about 10 mM to about 40 mM. Another
10 defining characteristic of T-type calcium channels is that they exhibit small single channel conductance. Thus, for example, a T-type channel exhibits a single channel conductance of from about 4 pS to about 12 pS (e.g., from about 6 pS to about 10 pS), and typically from about 7 pS to about 9 pS in a solution with a Ba^{2+} concentration of about 0.1 M.

15 The isolated or substantially purified nucleic acid of the present invention encodes all or part of any T-type calcium channel having at least one of the aforementioned electrophysiological properties when properly assembled within a cellular membrane. The general structure of calcium channels is summarized above and is otherwise known in the art. Thus, for example, the nucleic acid can encode one
20 of the four functional domains mentioned above. As used herein, a domain of a T-type calcium channel is any protein structure able to associate with three other domains to form a tetrameric body functioning as a T-type calcium channel. While the native T-type calcium channel structure includes all four domains in a single polypeptide (indicated in Figures 1A-1E), a domain can exist as a polypeptide species
25 separate from those containing the other domains. Such separate domains are able to associate within the plasma membrane to form a functional channel. Alternatively, where a plurality of domains are linked within a common polypeptide, the linkage can deviate substantially from the native linkage. Thus, for example, the domains can be linked by polypeptide sequences other than those sequences linking the domains in the
30 native protein (e.g., non-native polyglutamate linkages). Indeed, the domains themselves can include non-native linkages between membrane-spanning elements within the domains. Aside from these modifications, the nucleic acid can encode a chimeric calcium channel domain (or an entire channel) comprising a portion of a T-type calcium channel and a portion derived from another calcium channel (or other
35 channel) protein. For example, the chimera can include portions of domains from T-type channels responsible for low voltage gating and portions of domains from other calcium channels responsible for slow inactivation. Such a protein exhibiting T-type gating but longer inactivation kinetics would facilitate pharmacological research.

As mentioned, nucleic acids of the present invention can encode an entire T-type channel (i.e., a T-type channel protein comprising four functional domains). It has been discovered that at least three genes encoding T-type calcium channels exist in humans and rats (i.e., $\alpha 1G$ (or Ca_vT.1), $\alpha 1H$ (or Ca_vT.2), and $\alpha 1I$ (or Ca_vT.3)), and alternate splicing of these isoforms exist. Examples of the amino acid sequences of full-length T-type channels, and the sequences of suitable coding nucleic acids are set forth at SEQ ID NOs:1-8 ($\alpha 1G$ sequences), SEQ IS NOs:9-10 ($\alpha 1H$ sequences), and SEQ ID NOs: 11-12 ($\alpha 1I$ sequences). However, the invention is not limited to these exemplary sequences. Indeed, as mentioned, an amino acid sequence of a T-type calcium channel can vary from those listed, and it is within the state of the art to change a nucleotide sequence encoding a T-type channel to introduce mutations into the protein. Indeed, for conducting electrophysiological assays, it may be desirable to introduce mutations into such a protein. For example, mutations comprising insertions or deletions can be introduced on either the amino- or carboxy-terminus of the protein, or such mutations can be intrasequence insertions or deletions. Where the electrophysiological properties of the calcium channel are to be conserved, such mutations preferably are in regions other than the membrane spanning domains. However, in some applications (e.g., to decrease inactivation kinetics), the changes can be within the membrane-spanning regions. Moreover, as mentioned above, the sequence can form a protein having only one functional domain of a T-type calcium channel. Additionally, the sequence can also form a chimeric protein or domain, such as those described above.

Aside from insertions and deletion mutations of native T-type calcium channel sequences, a T-type calcium channel can include substitutions of amino acid residues, e.g., for those indicated in SEQ ID NOs:1-12. Preferably, and especially where such a substitution is within a membrane spanning region, the substitution is conservative. Thus, within membrane spanning domains, positively-charged residues (H, K, and R) preferably are only substituted with positively-charged residues; negatively-charged residues (D and E) preferably are only substituted with negatively-charged residues; neutral polar residues (C, G, N, Q, S, T, and Y) preferably are only substituted with neutral polar residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are only substituted with neutral non-polar residues. Preferably, any amino-acid substitution within the membrane-spanning regions does not alter this conservation. Most preferably, any substitution, deletion, or insertion does not alter the IVS4 domain. In each of the exemplary T-type calcium channel α subunit sequences, the putative IVS4 region comprises SEQ ID NO:13. Given the strong sequence conservation among families of voltage-gated ion channels, it is likely that this sequence or a derivative sequence, will be present in T-type channels. Thus, the

present invention provides any T-type calcium channel (or a nucleic acid encoding such a T-type calcium channel) comprising SEQ ID NO:13 or a sequence derived from SEQ ID NO:13 having conservative amino acid substitutions, as described above.

3 The nucleic acid of the present invention encoding all or a part of a T-type calcium channel can be isolated via any suitable method. For example, prior to the present invention, one of skill in the art could design a probe based on the sequence of known, non-T-type, calcium channels and use such probe to screen a genetic library. If such a screen were to identify a putative calcium channel, the researcher could then
10 attempt to clone the entire nucleic acid to characterize it. Similarly, prior to the present invention, to isolate a nucleic acid encoding a T-type calcium channel, one of skill in the art could consult publicly available databases containing DNA sequences (e.g., Genbank) to locate nucleic or amino acid sequences representing a portion of a T-type calcium channel protein or nucleic acid. However, such databases contain no
15 sequence for a full-length T-type calcium channel or identify any sequence as a T-type channel. Such methods assume that T-type calcium channels share sufficient sequence identity with known calcium channel nucleic acids to cross-hybridize, an assumption not supported by any published report. Moreover, prior to the present invention, no partial sequence in such databases was identified as corresponding to a
20 T-type calcium channel. Thus, prior to the present invention, the presence of partial sequences in the public DNA databases could facilitate the isolation of T-type calcium channels only with the exercise of a considerable degree of speculation on the part of the researcher.

By providing several sequences pertaining to T-type calcium channels and a
25 comparison presenting conserved regions and domains, the present invention greatly facilitates the isolation of other nucleic acids encoding T-type calcium channels (or derivatives thereof) with much less experimentation. Thus, while any of the methods discussed above can be employed to isolate other members of this genus, preferably, a nucleic acid encoding a T-type calcium channel is isolated by probing a genetic library
30 using a probe that hybridizes to a DNA encoding a peptide sequence contained in (or similar to) a known T-type calcium channel (e.g., SEQ ID NOs:1-12). To facilitate the isolation of a T-type calcium channel, the present invention provides an isolated polynucleotide hybridizing to a portion of the nucleic acid of the present invention encoding a T-type calcium channel (or a portion thereof). Thus, for example, the
35 present invention includes an isolated polynucleotide hybridizing to SEQ ID NO:1-12. The isolated polynucleotide can hybridize to all or any portion of the sequence encoding the T-type calcium channel.

To isolate such a polynucleotide, any portion of a sequence encoding a T-type calcium channel can be employed as a probe to screen a genetic library, and such screening can be accomplished by standard techniques known in the art. While the probe can hybridize to any portion of such a DNA, preferably the probe is designed to hybridize to a DNA encoding a polypeptide sequence that is highly conserved among T-type calcium channels but is less conserved between the genus of T-type calcium channels and other proteins. Such peptide sequences are readily apparent from the sequence comparison set forth in Figures 1A-1E. Generally, the specificity of hybridization in a genetic screen varies depending on the length of the probe and the stringency (e.g., temperature, salt and detergent concentration, etc.) of hybridization. Stringency of hybridization is broadly classified as "high," "moderate," or "low," and the parameters of these terms are well recognized in the art (see, e.g., Sambrook et al., "Molecular Cloning, a Laboratory Manual," Cold Spring Harbor Press, 1989). The isolated polynucleotide hybridizing to a portion of the nucleic acid encoding a T-type calcium channel can hybridize under any desired stringency conditions. However, for identifying other T-type channels, preferably, the hybridization occurs under moderate stringency, and most preferably under high stringency.

Of course, the isolated or substantially purified polynucleotide can itself be employed as a probe to screen a library as described to isolate a second nucleic acid. In such a screen, one of the polynucleotides will be complementary to a portion of the sequence encoding the T-type calcium channel, and the other isolated nucleic acid will be "sense." Preferably, one of the two isolated polynucleotides (the "sense" strand) itself encodes a T-type calcium channel, or at least one domain thereof. Such a sequence can be cloned to be operably linked to suitable regulatory elements, as described, to produce a T-type calcium channel. Thus, aside from using the nucleic acid of the present invention to produce a T-type calcium channel, the nucleic acids of the present invention are also useful for isolating other sequences encoding T-type calcium channels, or derivatives thereof.

However isolated, the isolated or substantially purified nucleic acid of the present invention is useful, in part, for producing all or a portion of a T-type calcium channel. Thus, the nucleic acid can be introduced into a suitable milieu for driving its expression. Because T-type channels are transmembrane proteins, preferably such a milieu is a living cell. However, it should be understood that the nucleic acid can also be expressed *in vitro* under conditions, such as those known in the art, suitable for *in vitro* transcription and translation. However produced, the present invention includes any protein, such as a recombinant protein or an isolated or substantially purified protein, including all or a portion of a T-type calcium channel or a protein derived from a T-type calcium channel.

For expression in a living cell, the nucleic acid must be introduced into the cell. As nucleic acids are generally introduced into cells as part of genetic vectors, the present invention provides a vector having a T-type calcium channel nucleic acid of the type described above. Any type of vector suitable for introducing the nucleic acid into a host cell is within the context of the present invention. Examples of such vectors include naked DNA and RNA vectors (such as oligonucleotides, plasmids, capped cRNA, etc.), viral vectors such as adeno-associated viral vectors (Berns et al., *Annals of the New York Academy of Sciences*, 772, 95-104 (1995)), adenoviral vectors (Bain et al., *Gene Therapy*, 1, S68 (1994)), herpesvirus vectors (Fink et al., *Ann. Rev. Neurosci.*, 19, 265-87 (1996)), packaged amplicons (Federoff et al., *Proc. Nat. Acad. Sci. USA*, 89, 1636-40 (1992)), papilloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors, vaccinia virus vectors, and other vectors. Once a given type of vector is selected, its genome must be manipulated for use as a background vector, after which it must be engineered to incorporate exogenous polynucleotides. Such manipulations are known in the art.

The vectors of the present invention are useful for introducing a nucleic acid encoding all or a portion of a T-type calcium channel into a host cell. Thus, the present invention provides a cell into which the vector of the present invention has been introduced. The host cell can be any cell suitable for expressing the nucleic acid (e.g., bacteria, insect cells, mammalian cells, etc.). The host cell can thus be *in vitro* or *in vivo*. Preferably the cells do not exhibit native T-type calcium current. A preferred cell type is HEK-293 cells because they contain genetic elements that facilitate the expression of transgenes from a variety of expression vectors. For facilitating electrophysiological recordings, oocytes (e.g., *Xenopus* oocytes) are preferred, as they are large and readily handled.

The vector can be introduced into the cell in any manner suitable for the cell type and vector employed. In one embodiment, the vector can be used to prepare an RNA transcript *in vitro* (e.g., a capped cRNA) which is then introduced into the host cell by standard methods (such as injection). Such techniques are preferred when the host cells do not actively transcribe DNA (such as oocytes). In other embodiments, a DNA vector is introduced into the cell such that it is transcribed within the cell. For example, the vector can be introduced into the cell such that it forms an extrachromosomal segment of genetic material in the cell, as is the case with many types of viral vectors. Alternatively, the vector can introduce the nucleic acid into the chromosomal DNA of the host cell.

Preferably, a cell into which the nucleic acid is introduced is also able to express the nucleic acid to produce the α subunit protein. The expression of the nucleic acid can be detected by probing the cell for the presence of T-type calcium

channel mRNA, such as via Northern hybridization analysis, in situ hybridization, etc. More preferably, however, the cell is able to express the nucleic acid to produce the protein including all or a portion of a T-type calcium channel. In such cells, expression of the nucleic acid is confirmed by detecting the protein, for example, by
5 probing cellular extracts with an antibody recognizing the protein (e.g., on a Western blot, etc.).

In the membrane of the cell producing the protein, the expressed protein contributes to the formation of a functional calcium channel. Where the protein encodes an entire α subunit, the full protein will possess some or all of the
10 electrophysiological properties of T-type calcium channels described above. Where the protein encodes less than an entire channel α subunit (e.g., a domain), the protein will aggregate with other constituent domains in the membrane to form a functional channel. Thus, the presence of the protein can be detected by assaying the cell for T-type calcium channel activity. Indeed, assaying for channel activity serves to
15 determine whether a nucleic acid encoding a putative calcium channel, in fact, encodes a species of T-type channel (as opposed to a member of another genus of calcium channels). For example, when large cells (e.g., oocytes) are used as the host cells, the electrophysiological properties of the channel can be investigated. Thus, the membrane activity of whole cells expressing the nucleic acid can be measured
20 directly, such as via patch clamp techniques using a voltage clamp electrode and a current electrode (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). Alternatively, the activity of single channels can be measured, such as with a standard depolarizing bath and pipette solutions (Lacerda et al., *Biophys. J.*, 66, 183-43 (1994)). However measured, the properties of cells into which the putative nucleic
25 acid is introduced are compared to the channel conductance, voltage dependency, activation kinetics, inactivation kinetics, or tail current known for T-type channels and discussed above. A measure of current density (e.g., pA/pF) can also be used to assess the level of gene expression in the cells, normalizing for cellular volume.

While, in accordance with the present invention, an isolated cell into which the
30 T-type calcium channel nucleic acid has been introduced (and preferably stably expressing the nucleic acid to produce the protein) can be prepared, preferably, such transfection protocols result in a population consisting essentially of such transfected cells. For standardizing the results of many experiments, it is even more desirable to employ an established cell line consisting essentially of such cells. Preferably, for use
35 in high throughput assays, cell lines stably expressing a T-type calcium channel exhibit a current density of at least about 40 pA/pF (e.g., at least about 45 pA/pF), such as about 50 pA/pF or even 55 pA/pF or higher. Preferably, a cell line in accordance with the present invention is able to propagate the nucleic acid through

several passages (e.g., for at least 10 passages), and, preferably, the nucleic acid is stably integrated into the chromosomes of such cells. Thus, the cell line can propagate the nucleic acid for at least 20 passages, and more preferably significantly more than 20 passages (e.g., at least about 25 passages, or even more).

5 Regardless of the cell system, the ability to express a T-type calcium channel nucleic acid within host cells to produce an active channel permits the channel to be further studied. In this regard, the present invention provides a method of identifying a drug which affects T-type calcium channels. The method involves first expressing a T-type calcium channel in a cell to produce an active channel, as herein described.

10 The cell expressing the channel is then exposed to a solution containing a putative drug for interfering with the channel. Thereafter, the presence or absence of calcium flux in response to a change in membrane potential is assayed. Any such assay can be employed within the context of the present invention, (e.g., using labile dyes, radioisotopes (e.g., ^{45}Ca), recording electrophysiological changes in the membrane, etc.). A quick method of assaying for calcium flux is first to introduce a
15 calcium-sensitive labile dye into the cells. For example, the dye can be one such as those that fluoresce or change color in the presence of calcium, many of which are known to those of skill in the art (e.g., Indo-1). Thereafter, the cells are exposed to a depolarizing solution containing high (e.g., about 50 mM) potassium concentration and a drug, and the reaction of the labile dye is compared to control cells. Using a
20 labile dye affords the ability to assay many putative drugs quickly in a high throughput assay for putative drugs affecting T-type channels. For example, the initial screening can be carried out in 96 well plates. Moreover, dose-response data can be readily generated by exposing the cells to several concentrations of the same putative
25 drug.

 Once a putative drug is detected, its effect on the electrophysiology of the cell (e.g., single channel conductance, voltage dependency, activation kinetics, inactivation kinetics, and tail current of the cells) can be investigated in detail. Generally, the effect of the putative drug on T-type calcium currents is assessed by
30 measuring the various electrophysiological parameters in the presence of various concentrations of the drugs and comparing the data to untreated (or sham-treated) control cells. Cells preferably are maintained in a continuous perfusion chamber during such experiments to facilitate changing solutions. The inventive method of identifying a drug which affects T-type calcium channels can employ any nucleic acid
35 encoding a T-type calcium channel (or derivative thereof), such as those nucleic acids described herein. In fact, as several isoforms of T-type channel exist, the assay method can be repeated using nucleic acids encoding different isoforms to identify

drugs that preferentially target a given isoform, or drugs which affect more than one isoform of T-type calcium channels.

Aside from affording an *in vitro* assay for detecting potential therapeutic or investigative drugs targeting T-type calcium channels, the method of expressing the T-type calcium channel nucleic acid can also be used *in vivo*. For example, as mentioned, several neurological and muscular diseases or disorders have implicated mutations affecting native nucleic acids encoding T-type calcium channels. The present invention, thus, provides a method of treating a disease or disorder associated with a deficiency in a native T-type calcium channel nucleic acid. The method involves introducing a vector having the T-type calcium channel nucleic acid into cells of a host in which native expression of the nucleic acid is deficient. Thus, for example, for treating cardiomyopathy associated with deficiencies in T-type calcium channels, the vector is introduced into myocardial cells. Similarly, for treating forms of epilepsy associated with deficiencies in T-type calcium channels, the vector is introduced into neurons (e.g., thalamic neurons). Within the target cells, the nucleic acid within the vector is expressed to produce active T-type calcium channel. By similar methods, an nucleic acid having a sequence antisense to a sequence encoding a T-type calcium channel (or a portion thereof) can be expressed within a cell. The presence of an antisense sequence can down-regulate the expression of native T-type calcium channel genes by hybridizing to T-type channel mRNA within the cell. Thus, the present invention is useful to treating disorders associated with over-expression of T-type calcium channels.

T-type channel proteins (such as whole T-type calcium channels, domains of such channels, chimeras including portions of T-type calcium channels, etc.) can be employed to generate antibodies (e.g., immunoglobulins) to T-type calcium channels. Thus, the present invention provides an isolated and substantially purified antibody molecule recognizing an epitope on a T-type calcium channel. Such antibodies can be monoclonal antibodies or polyclonal antisera. Antibodies recognizing T-type calcium channels can be used to purify the channels from cell extracts or other solutions by standard methodologies (e.g., immunoprecipitation). Moreover, depending on the location of the epitopes for the antibodies on the T-type calcium channel, the antibodies can be used to affect the channel proteins present on the surface of cells. Thus, antibodies directed to T-type calcium channels are potential reagents for studying the channels as well as for therapy.

Such antibodies can be produced by any suitable method, many of which are well known in the art. Thus, for example, the antibodies can comprise polyclonal antisera obtained from inoculated animals. Alternatively, the antibody molecules can be monoclonal antibodies obtained from a cell line (e.g., a hybridoma cell line). Thus,

the present invention provides a cell which produces such antibodies. Such a cell can be *in vitro* or *in vivo*; however, where the cell is *in vitro*, preferably it is within an established cell line consisting essentially of such cells.

Several examples are presented below to illustrate the invention. Taken
5 together, the examples demonstrate the cloning of twelve novel proteins and their characterization as T-type calcium channel α subunits. These examples are included here for purely illustrative purposes; as such, they are not to be construed so as to limit the scope of any aspect of the invention.

Many procedures employed in the following examples are techniques routinely
10 performed by one of ordinary skill in the art (see generally Sambrook et al., *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)) and are not discussed in detail. However, some reagents and methods deserve specific description. Thus, for example, *in vitro* translation and expression were conducted as described previously (Schneider et al., *Receptors and Channels*, 2,
15 255-70 (1995)). *Xenopus laevis* oocytes were prepared as described previously (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). To express proteins, 10 or 30 ng of capped cRNA was injected into the oocytes in a volume of 50 nl. For single channel recording, oocytes were injected with 100 ng capped cRNA and incubated for one week prior to assay.

20 Cells were voltage clamped using a two-microelectrode voltage clamp amplifier as described (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). The standard bath solution contained the following: 40 mM Ba(OH)₂, 50 mM NaOH, 1 mM KOH, 0.1 mM EDTA, and 5 mM HEPES, adjusted to pH 7.4 with methanesulfonate. The osmolality of the 2 mM Ba²⁺ and 10 mM Ba²⁺ solutions was
25 balanced by increasing the NaOH concentration as described (Lory et al., *J. Physiol. (London)*, 429, 95-112 (1990)). Voltage and current electrodes (1.5-1.8 M tip resistance) were filled with 3 M KCl. Except as noted, data were acquired at 4 kHz using the pCLAMP system, and filtered at 1 kHz. Data were analyzed using pCLAMP software. Boltzman fits and linear regression were calculated using Prism.

30 EXAMPLE 1

This example demonstrates the cloning and characterization of putative T-type calcium channels.

A search of the Genbank library was conducted to identify clones identified as
35 having some degree of homology to known calcium channel sequences. The search identified an expressed sequence tagged (EST) partial sequence in a human brain clone (H06096), which was used as a probe to screen a λ gt10 cDNA library prepared

from rat brain. Successive screening of the cDNA library identified five overlapping clones which were aligned to construct an entire cDNA sequence, termed $\alpha 1G$.

The $\alpha 1G$ cDNA was cloned into the pSP72TM vector and sequenced by standard computer-assisted sequencing. Using the $\alpha 1G$ cDNA, the amino acid sequence of the $\alpha 1G$ protein was deduced and compared to the sequences of other known calcium channel α subunits. By similar methods, homologous human (H19230 and R19524) and mouse (AA286626) EST clones were also identified and partially sequenced, and alternately spliced variants were identified. The deduced cDNA and amino acid sequences for eight full-length $\alpha 1G$ T-type channels are set forth, respectively, as SEQ ID NOs:1-8.

A second T-type calcium channel, termed $\alpha 1H$, was isolated by screening a human heart cDNA library with a fragment of the $\alpha 1G$ sequence. An alternately spliced isoform was also identified. The full-length cDNA and amino acid sequences for these $\alpha 1H$ T-type channels are set forth, respectively, as SEQ ID NOs:9 and 10.

A third T-type calcium channel, termed $\alpha 1I$, was isolated by screening a rat brain cDNA library at low stringency using a fragment of the rat $\alpha 1G$ gene. Fifty plaques were identified, many of which were not detected in a second screening. A third screening with a fragment from $\alpha 1H$ identified two clones. Subsequent screening, and the use of the GenBank database, led to the identification of the full length rat and human cDNA and amino acid sequences, set forth at SEQ ID NOs: 11 and 12, respectively.

The $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ amino acid sequences were compared to each other and a known calcium channel ($\alpha 1E$) to investigate the conservation of protein structure and function. The comparison indicates that the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ amino acid sequences within the putative membrane-spanning domains are about 90 % identical to each other, while the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ sequences are only roughly 40 % identical to the $\alpha 1E$ clone.

Figures 1A-1E indicate this conservation between the proteins. The conservation of charged residues, particularly in the S4 domains, is consistent with the role of the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins as ion channels. However, two of the glutamates associated with ion specificity in other calcium channels have been replaced with aspartate, suggesting altered ion selectivity. Strikingly, $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ display only low homology to sequences linking the membrane-spanning regions within each domain, and even less homology between the intracellular loops linking domains. Notably, neither $\alpha 1G$, $\alpha 1H$, nor $\alpha 1I$ possesses sequences known to bind β subunits or Ca^{2+} ions.

EXAMPLE 2

This example demonstrates the production of cell lines stably expressing the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins.

HEK-293 cells were transfected with either the rat $\alpha 1G$ cDNA (SEQ ID NO:1), the human $\alpha 1H$ cDNA (SEQ ID NO:9), or the rat $\alpha 1I$ cDNA (SEQ ID NO:11). As a control, cells were also transfected with human $\alpha 1E$ plus human $\beta 3$ (Schneider et al., *Receptors Channels*, 2, 255-70 (1994); Murakami et al., *Eur. J. Biochem.*, 236, 138-43 (1996)). The DNA constructs included a neomycin resistance gene conferring resistance to G418. The cells were cultured under standard conditions using medium containing G418 to select for stable transformants.

Surviving clones were expanded and assayed for electrophysiological activity to determine the presence of channels within the membrane. Whole-cell currents were recorded from ruptured patches using an Axopatch 200A amplifier, Digidata 1200 A/D converter, and pCLAMP 6.0 software. Data were digitized at 2 kHz and filtered at 1 kHz or off-line. All experiments were performed at room temperature. Pipettes were made out of TW-150-6 capillary tubing (World Precision Instruments, Inc., Sarasota, FL), using a Model P-97 Flaming-Brown pipette puller (Sutter Instrument Co., Novato, CA). The internal pipette solution contained the following: 55 mM CsCl, 75 mM CsSO₄, 10 mM MgCl₂, 0.1 mM EGTA, 10 mM HEPES, pH adjusted to 7.2 with CsOH. The external Tyrodes solution was the following: 140 mM NaCl, 6 mM KCl, 2 mM CaCl₂, 10 mM glucose, 5 mM HEPES, pH 7.4. The recording solution contained the following: 10 mM BaCl₂ solution (or 2 mM CaCl₂), 140 mM tetraethylammonium (TEA) chloride, 5 mM CsCl, 1 mM MgCl₂, 5 mM glucose, and 10 mM HEPES, pH adjusted to 7.4 with TEA-OH. Under these solution conditions the pipette resistance was typically 1.5-2.5 M Ω . Cell capacitance was measured by integrating the charging current during a 10 mV hyperpolarizing pulse (holding potential -80 mV).

Using these recording techniques, values for pA/pF were obtained for each cell line, which is a measure of current density normalizing for cell size. One clone (#N2) expressed the rat $\alpha 1G$ protein and has a current density of 42 pA/pF. Another clone (#13), expressed the human $\alpha 1H$ protein and exhibited a current density of 53 pA/pF. Three clones (#11, #19, and #25) expressed the rat $\alpha 1I$ protein and exhibited current densities of 40 pA/pF, 45 pA/pF, and 55 pA/pF, respectively.

EXAMPLE 3

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type current-voltage relationships.

Current traces were elicited by depolarizing voltage clamp pulses of the membranes of cells. The $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins were produced in *Xenopus laevis* oocytes by linearizing the DNA vectors containing the coding sequences, and transcribing the coding sequences *in vitro* by standard methods. Oocytes were then injected with the capped RNA.

Figures 2A-2E depict data obtained from these experiments using cells injected with $\alpha 1G$ (Figure 2A), $\alpha 1H$ (Figure 2B), and $\alpha 1I$ (Figure 2C) and $\alpha 1E$ (Figure 2D). These data indicate that cells expressing $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ exhibit T-type calcium current, while oocytes expressing $\alpha 1E$ as well as uninjected oocytes (Figure 6A) do not.

Current voltage curves were developed using cells injected with $\alpha 1G$, $\alpha 1H$, $\alpha 1I$, and $\alpha 1E$. Figures 3A depicts such data generated in a 10 mM Ba^{2+} test solution. These data were transformed into conductance and fit with a Boltzman equation to determine the midpoint of activation ($V_{0.5}$). Gating potentials for $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ (-38 ± 1 mV, $n=8$, -44 mV ± 1 mV, $n=10$, and -31 mV ± 1 mV, $n=6$, respectively) were in accordance with the gating potential measured for the HEK-293 cells (-41 ± 1 mV, $n=10$), while $\alpha 1E$ required significantly more positive potentials to open (-2.6 mV $\pm .4$ mV, $n=3$).

To compare the characteristics with published values (Huguenard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)), the $\alpha 1G$ current was recorded at varying concentrations of Ba^{2+} . As indicated in Figure 3B, in solutions containing 2 mM Ba^{2+} , $V_{0.5}$ was -46.5 mV, and the slope factor (k) was 6.6 ($n=7$). However, when the Ba^{2+} concentration was 40 mM, $V_{0.5}$ was recorded at -21 mV, presumably due to the results of barium on surface charge screening (see, e.g., Wilson et al., *J. Membrane Biol.*, 72, 117-30 (1983)). Similar values were recorded for $\alpha 1H$ and $\alpha 1I$.

These results indicate that $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ are low-voltage activated calcium channels (i.e., from about -60 mV to about -30 mV in 10 mM Ba^{2+}).

EXAMPLE 4

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type tail current.

Tail current was measured at -90 mV after first opening the channels with a voltage step to -10 mV. The voltage-dependence of tail current in cells expressing $\alpha 1G$ (oocytes), $\alpha 1H$ (HEK 293 cells), and $\alpha 1I$ (HEK 293 cells) was measured at varying test potentials. As a control, tail current was also measured from a high voltage activated channel $\alpha 1E$, which. Raw data from recordings data were fit with a single exponential and plotted as a function of depolarization potential (Figure 4).

These results demonstrate that the tail currents for the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ calcium channels are voltage-dependent, consistent with known T-type calcium tail currents. Additionally, these data demonstrate that the tail current for each of the cloned channels is between about 1 ms and about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

EXAMPLE 5

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type single channel conductance.

Measurement of single channel conductance is complicated by the low probability of channel opening at negative potentials when the driving force is large. Thus, single channel conductance was measured similarly for measurements of tail currents to enhance channel opening at negative potentials. Single channels were measured with standard depolarizing bath and pipette (115 mM $BaCl_2$, 1 mM EGTA, and 10 mM HEPES, pH 7.4) solutions (Lacerda et al., *Biophys. J.*, 66, 1833-43 (1994)). Data were analyzed with TRANSIT (VanDongan, *Biophys. J.*, 70, 1303-15 (1996)). Single channel amplitudes were measured by averaging the values obtained from Gaussian fits to all-points histograms of traces with openings, selected openings, or amplitude histograms of idealized openings. It has been reported that some oocytes contain a native 9 pS channel. These endogenous channels can be distinguished by their 2-fold larger current amplitudes at the potentials tested (e.g., -20 mV, $i = 0.8$ for endogenous channels as opposed to 0.4 pA for $\alpha 1G$). However, such endogenous channels were not detected either at the whole cell or single channel level in the oocytes tested.

Current through the main open state of each open channel was measured at each potential and plotted against each test potential. Single channel currents for several patches were then averaged and plotted as a function of test potential, wherein the slope of the plot indicated the single channel conductance. The average slope conductance of the $\alpha 1G$ channel was measured at 7.5 ± 1.5 pS, which corresponds with the reported values for T-type calcium channels (Hugenard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)). Similar results were also obtained with both $\alpha 1H$ (10.8 ± 1.4 pS). Data collected from recordings of the $\alpha 1I$ channels indicate that they open to two distinct amplitudes. The conductance for the small amplitude $\alpha 1I$ openings was measured at 3.9 ± 0.5 pS, while that for the large $\alpha 1I$ openings was measured at 11.4 ± 0.5 pS).

These results indicate that the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins exhibit T-type single-channel conductance (e.g., from about 4 to about 12 pS).

EXAMPLE 6

This example demonstrates that a cloned T-type calcium channel can be used for identifying a drug which affects T-type calcium channels.

5 HEK-293 cells were subjected to treatment as indicated above in Example 3, except that an experimental group of cells were exposed to a solution containing 1 μ M mibefradil, a known inhibitor of T-type calcium current. As depicted in Figure 5A, the presence of mibefradil almost completely abolished T-type current in cells
10 expressing $\alpha 1G$. Cells expressing either $\alpha 1G$ or $\alpha 1H$ were similarly treated using various concentrations of mibefradil to determine a dose-response relationship. These results, depicted in Figure 5B, demonstrate that about 50% inhibition was achieved at a mibefradil concentration of 1 μ M.

15 All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this
20 invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

What is claimed is:

1. A isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α subunit.
- 5 2. The nucleic acid of claim 1, wherein said protein comprises an entire T-type calcium channel α subunit.
3. The nucleic acid of claim 2, wherein said protein comprises SEQ ID NO:13.
4. The nucleic acid of any of claims 1-3, wherein said calcium channel begins
10 to gate from about -60 mV to about -30 mV in 2 mM Ba^{2+} .
5. The nucleic acid of any of claims 1-4, wherein said calcium channel exhibits a tail current of from about 1 ms to about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.
- 15 6. The nucleic acid of any of claims 1-5, wherein said calcium channel exhibits a single channel conductance of from about 4 pS to about 11 pS in a solution with a barium ion concentration of about 100 mM.
7. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of any of claims 1-6.
- 20 8. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of claim 7.
9. The nucleic acid of claim 8 comprising a sequence encoding at least one domain of a T-type calcium channel α subunit.
10. A vector comprising the nucleic acid of any of claims 1-9.
- 25 11. A cell into which the vector of claim 10 has been introduced.
12. The cell of claim 11, which expresses said nucleic acid to produce said protein.
13. The cell of claim 11 or 12, which stably expresses said nucleic acid to produce said protein.
- 30 14. A population of cells consisting essentially of cells according to any of claims 11-13.
15. An established cell line consisting essentially of cells according to any of claims 11-13.
16. A method of identifying a drug which affects T-type calcium channels, said method comprising expressing a T-type calcium channel in a cell, exposing said
35 cell to a putative drug, and measuring the calcium flux through the membrane of said cell in response to a change in membrane potential.

17. The method of claim 16, wherein said calcium flux is assayed by using a calcium-sensitive labile dye within said cell.

18. The method of claim 16, wherein said calcium flux is assayed by measuring the electrophysiological properties of said cell.

3 19. The method of claim 16, wherein said calcium channel comprises SEQ ID NO:13.

20. An isolated or substantially purified immunoglobulin recognizing an epitope on a T-type calcium channel protein.

21. A cell *in vitro* which produces the immunoglobulin of claim 20.

10 22. An established cell line consisting essentially of cells according to claim 21.

hCavT1a MDEEDGACAEZESQPR-----SFMINDLSGACGPPCPGSAEKOPGSADEAEGLPYPALAFVVFILSQDSPRSMCLRTVCNFW
 rCavT1a MDEEDGACAEZESQPR-----SFTQLNDLSGACGPPGSGTEKOPGSADEAEGLPYPALAPVVFILSQDSPRSMCLRTVCNFW
 hCavT2a MTEGARAADDEVPLGRFPWPCVGGGVFGEPRGACRCCGCFELGVSPSEPAERCAELGAEZEEQRYYPALAAATVFCLOQTPRSMCLRLVCNFW
 hCavT3 MAESAPFSSAAA-----FAAPCVTTTQPSRSPSPSPGCLLEFEDGADPHVPHPOLAPIAFFCLNQTTSPRSMCLRMVCNFW
 rCavT3 MADSNLPSSAAAP-----APEPG---ITEQPCRSPPSPSPSPGCLLEFEGTGHVPHPOLAPVAFTNLEQTTPRSMCLRMVCNFW

181 182 183

hCavT1a FERISMLVILLNCVTILGMFRPCEDIACDSQRCHILQAEDDFIFAFFAVEMVVRWVALGIFGKKCYLGGTWNRLDFFIVIAGMLEYSIDLQNVSFSAVRTV
 rCavT1a FERVSMLVILLNCVTILGMFRPCEDIACDSQRCHILQAEDDFIFAFFAVEMVVRWVALGIFGKKCYLGGTWNRLDFFIVIAGMLEYSIDLQNVSFSAVRTV
 hCavT2a FEHVSMVILLNCVTILGMFRPCEDVECSERCMILEADAFIFAFFAVEMVVRWVALGIFGKKCYLGGTWNRLDFFIVVACSMEYSIDGHNVSLSAIRTV
 hCavT3 FECVSMLVILLNCVTILGMFRPCEDMDCLSDCKIMQVDDFIFIFFAMEMVLRWVALGIFGKKCYLGGTWNRLDFFIVRAGWEYSIDLQNLNLSAIRTV
 rCavT3 FECVSMLVILLNCVTILGMFRPCEDMDCLSDCKILQVDDDFIFIFFAMEMVLRWVALGIFGKKCYLGGTWNRLDFFIVRAGWEYSIDLQNLNLSAIRTV

184 185

hCavT1a KVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVILLLCFFVFFIFGIVGVQIMAGLLRNRCFLPENFSPLSVD-LERYVQTEMEDESPFFICSQPRENCHRS
 rCavT1a KVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVILLLCFFVFFIFGIVGVQIMAGLLRNRCFLPENFSPLSVD-LERYVQTEMEDESPFFICSQPRENCHRS
 hCavT2a KVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVILLLCFFVFFIFGIVGVQIMAGLLRNRCFLPENFSPLSVD-LERYVQTEMEDESPFFICSQPRENCHRS
 hCavT3 KVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVILLLCFFVFFIFGIVGVQIMAGLLRNRCFLPENFSPLSVD-LERYVQTEMEDESPFFICSQPRENCHRS
 rCavT3 KVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVILLLCFFVFFIFGIVGVQIMAGLLRNRCFLPENFSPLSVD-LERYVQTEMEDESPFFICSQPRENCHRS

IP LOOP

hCavT1a CRSVPTLRGCG-----GGGPECGLDYEAVSSSMTTCVNNQYITWCSAGEHNPERKCAINFDNIGYAMIAIFQVITILEGWYDIMFYMDAHSFYNFIFYFI
 rCavT1a CRSVPTLRGCG-----GGGPPCSLDYETNSSSMTTCVNNQYITWCSAGEHNPERKCAINFDNIGYAMIAIFQVITILEGWYDIMFYMDAHSFYNFIFYFI
 hCavT2a CSHIPGRROVENPCTLSWEA-YTQPOAGGVGAASNACINNNQYINVCSSDSNPNHSAINTDTCYAMIAIFQVITILEGWYDIMFYMDAHSFYNFIFYFI
 hCavT3 CHEIPPLKEQRECCLSKODVYDFGACRQDILNASGLCVNNNRYINVCSTSANPHKCAINFDNIGYAMIAIFQVITILEGWYDIMFYMDAHSFYNFIFYFI
 rCavT3 CHEIPPLKEQRECCLSKODVYDFGACRQDILNASGLCVNNNRYINVCSTSANPHKCAINFDNIGYAMIAIFQVITILEGWYDIMFYMDAHSFYNFIFYFI

186

hCavT1a LLIIVGSFFMINCLVVIATQFSETKQRESQIMQEVRLSNASTIASFSEPGSCYEEELKLVLVYILRKARRLAQVSRACVTVCLLSSPAPLQOQET
 rCavT1a LLIIVGSFFMINCLVVIATQFSETKQRESQIMQEVRLSNASTIASFSEPGSCYEEELKLVLVYILRKARRLAQVSRACVTVCLLSSPAPLQOQET
 hCavT2a LLIIVGSFFMINCLVVIATQFSETKQRESQIMQEVRLSNASTIASFSEPGSCYEEELKLVLVYILRKARRLAQVSRACVTVCLLSSPAPLQOQET
 hCavT3 LLIIVGSFFMINCLVVIATQFSETKQRESQIMQEVRLSNASTIASFSEPGSCYEEELKLVLVYILRKARRLAQVSRACVTVCLLSSPAPLQOQET
 rCavT3 LLIIVGSFFMINCLVVIATQFSETKQRESQIMQEVRLSNASTIASFSEPGSCYEEELKLVLVYILRKARRLAQVSRACVTVCLLSSPAPLQOQET

Fig. 1A

hCavT1a QPSSSCSRSHRLSVNHLVNNHHNNHHNNHXLNMCNTRLAPRASPEIQORDANGSRRLMLPPSTPALSACAFEGGA-----E.SVHSFYTHADCHLEPVRC
rCavT1a QPSSGCTNSHRLSVNHLVNNHHNNHHNNHLCNCTLVVPRASPEIQORDANGSRRLMLPPSTPTFPSCGPPRGA-----E.SVHSFYTHADCHLEPVRC
hCavT2a CHRQZRACRHTASVNNHLVNNHHNNHHNNHNFHSNCSNRPFCGPEFCACDTRLVRAGAEFFPFGCGCPDAESVHSIYNHACNIEGFPQERABVSTCRSHCEG
hCavT3
rCavT3
hCavT1a QAPPPRSPSEASCHTVCSCKVYPTVHTSPRETKELKALVEVAASSPPHTLSLN-IPFGPVSSMHKLLLEQTSTGACQSSCKISSFCLKADSGACGPDSC
rCavT1a QAFFPHCFSEASCRVCSCKVYPTVHTSPREPIADKALVEVAPSPPPHTLSLN-IPFGPFSMHKLLLEQTSTGACHSSCKISSFCSKADSGACGPDSC
hCavT2a QPQACHRACHHELPHDPAIRGGQQRQCHQFRTQCEVCRWTAHRGHOPLSNPSOPYEKTPHVAGEHGLQAPGHSLSVFCPLPSPACTLTTELKSC
hCavT3 ALGTEAPAPAKFPGHAKENHYQLCFQNSPLDAPHTLVQFIFATLASDPASC
rCavT3 AMGCGTAPAPAKFPGHAKEPESHOKLCRPHSPLEDTHTLVQFISAILASDPSSC
hCavT1a PYCARA-GACEVELADREMFOSDSEAVIBETQDAQHSDLRDPS-----RR-QRSLGPDAPSSVLAPFWLLICDITFRKIVDSKYFNGCIM
rCavT1a PYCART-GACEFESADHVMEDESEAVIBETQDAQHSDLRDPS-----RRQRSLGPDAPSSVLAPFWLLICDITFRKIVDSKYFNGCIM
hCavT2a PYCTRALEDPEGLSCSECDSDGCGVETFTQDVHRGDEMDFTRPRANDTPGFCGCPQBARAARPGEPKMMKMLVWTFPSCKLRIVDSKYFNGCIM
hCavT3 PCQNHEDGRPPSGHGSTDSQEGS-----GSGSSAGDEZAGCHGABESSEDGASSELGKEEHEEEOADGAVWLCEDPWEYTRAKLACIVDSKYFNGCIM
rCavT3 PHOHEACRRPEGLSGTDSGOEGS-----GSGGSA--EAEANGDGLSSEDEGVSSDLGKEEZE--DGAARLCEDPWEYTRAKLRGIVDSKYFNGCIM
hCavT1a IAILVNTLSMCIETHEQPEELTNALEISNIVFTSLFALEMILLKLVYGTGCIKNPNYNIDGVIIVISWEIVGQOQCGLSVLATFRMLKVLKLVRELP
rCavT1a IAILVNTLSMCIETHEQPEELTNALEISNIVFTSLFALEMILLKLVYGTGCIKNPNYNIDGVIIVISWEIVGQOQCGLSVLATFRMLKVLKLVRELP
hCavT2a MAILVNTLSMGEVYHEQPEELTNALEISNIVFTSMFALEMILLKILACGFLGCIKNPNYNIDGVIIVISWEIVGQOQCGLSVLATFRMLKVLKLVRELP
hCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMILLKLAAGFLDYLRPNYNIDFSIIVISWEIVGQOQCGLSVLATFRMLKVLKLVRELP
rCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMILLKLAAGFLDYLRPNYNIDFSIIVISWEIVGQOQCGLSVLATFRMLKVLKLVRELP
hCavT1a LORQLVVLKTMENNVATFCNMLMFIFIFISILGMIHFGCKFASERD-GDTLDRKNFDSLLMAIVTVFOILTQEDMKNKVLNMGMASTSSWAALIFYALMT
rCavT1a LORQLVVLKTMENNVATFCMLMLFIFIFISILGMIHFGCKFASERD-GDTLDRKNFDSLLMAIVTVFOILTQEDMKNKVLNMGMASTSSWAALIFYALMT
hCavT2a LRRQLVVLVNTENNVATFCMLMLFIFIFISILGMIHFGCKFSLKDTGDTVDPRKNFDSLLMAIVTVFOILTQEDMKNVVLNMGMASTSSWAALIFYALMT
hCavT3 LRRQLVVLKTMENNVATFCMLMLFIFIFISILGMIHFGCKFSLKDTGDTVDPRKNFDSLLMAIVTVFOILTQEDMKNVVLNMGMASTSSWAALIFYALMT
rCavT3 LRRQLVVLKTMENNVATFCNMLMFIFIFISILGMIHFGCKFSLKDTGDTVDPRKNFDSLLMAIVTVFOILTQEDMKNVVLNMGMASTSSWAALIFYALMT

12
20

11185

hCavT1a FGNVLFNLLVAIIIVGCFQAGCDANKSESEPDFTSPSIDGDCDKKRCIALVSLGHNPELRKSLLPFL-----IHTAATPMSLPKSTSTGLGEALGPASR
 rCavT1a FGNVLFNLLVAIIIVGCFQAGCDANKSESEPDFTSPSYDQCDKKRRIALVALGZHAELKSLLPFL-----IHTAATPMSEHKSSSTGVEALGOSGR
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 hCavT3 FGNVLFNLLVAIIIVGCFQAGCDANKSYSDQSSNTEEFKLGQGLDSSGPKLCLPIPMTPNGHLDPLSLGCHLFGAGACGAPAPRLSLQFQFQFVAL
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11184

11185

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Fig. 1C

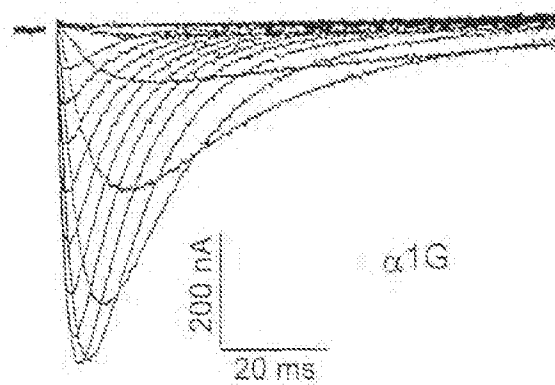
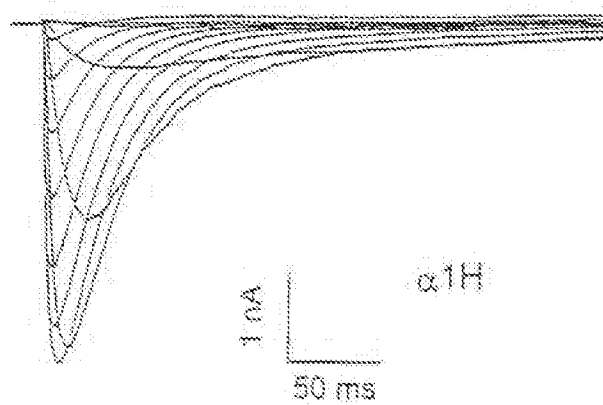
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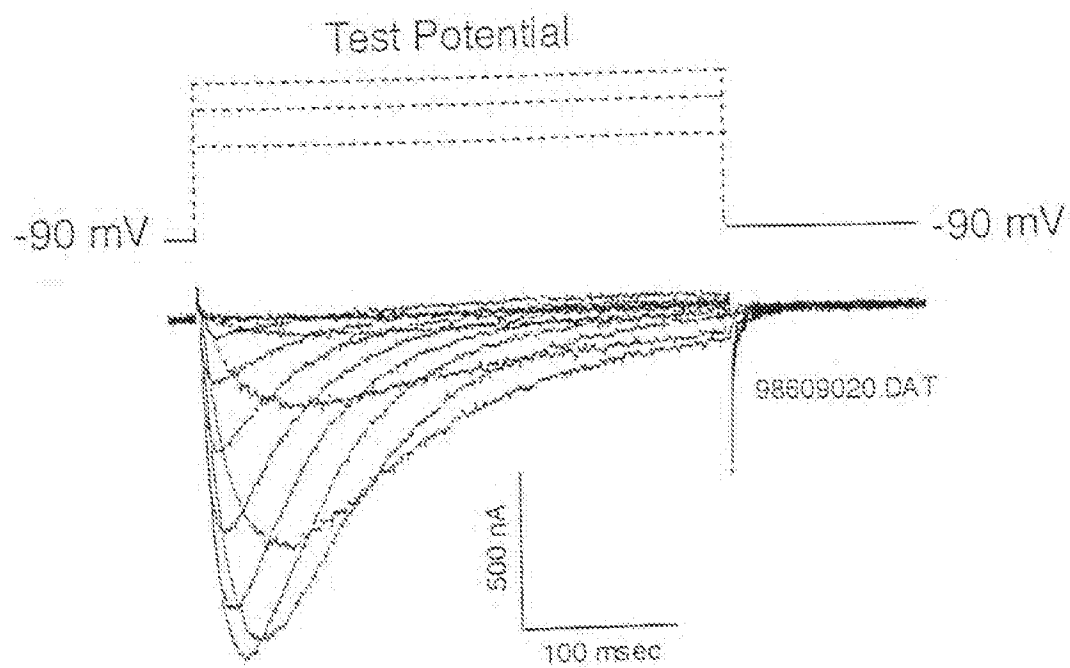
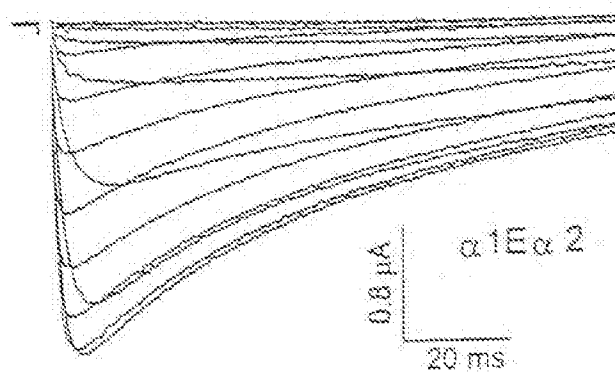
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 rCa,T1a DILLAEVSGPSPPLARAYSPWQSSSTQAQQHRSKSHKSNMTFPAPCPGPEPWCXGPPETRSLSLELDTLSWISGDLLEPFGQEEPPSPKOLKNCYSVE
 hCa,T2a -----PLHALSPRGSTARSPSLRLCRQEAHVHDSLKRLTALGTFWILOSLVKKR (SEQ ID NO:9)
 hCa,T3 -----LEGELTIIDNLGSGIFHHYSSPAGCKKCHNDKQETGTPPSCWVT (SEQ ID NO:11)
 rCa,T3 -----LEGELTIIDNLGSGVTFHHYASPDCCCKCHNDKQETGLHESCWGT (SEQ ID NO:12)

 hCa,T1a AQSCQSRPTSMWLDQREHSIAVSCLDGSGQPHLCTDPNLCGQPLGCPGSRPMKGLSPPSITIDPESQGPRTTPSPGICLRRAAPSSDSKDFLASGPEE
 rCa,T1a TQSCRRRPTSMWLDQREHSIAVSCLDGSGQPHLCTDPNLCGQPLGCPGSRPMKGLSPPSITIDPESQGPRTTPSPGICLRRAAPSSDSKDFLASGPEE

 hCa,T1a SMAASPSPKKVLSLGLSDDPADLDP (SEQ ID NO:1)
 rCa,T1a STAASPSPKKVLSLGLSDDPADLDP (SEQ ID NO:5)

Fig. 1E

**Figure 2A****Figure 2B**

**Figure 2C****Figure 2D**

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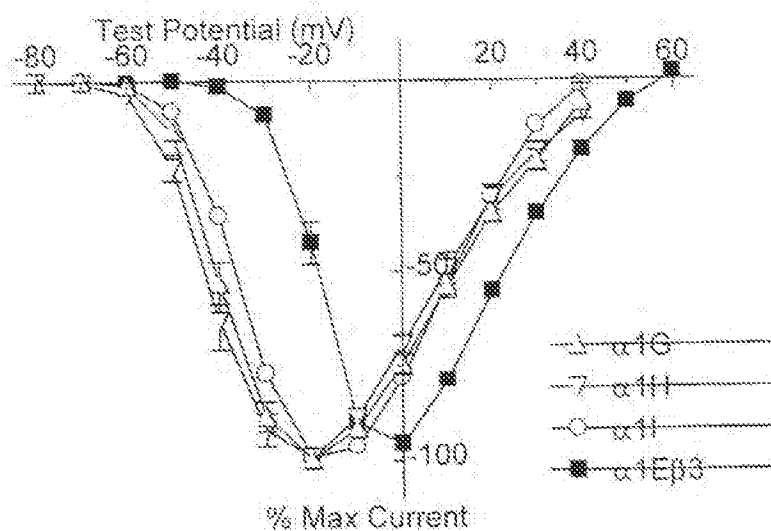


Figure 3A

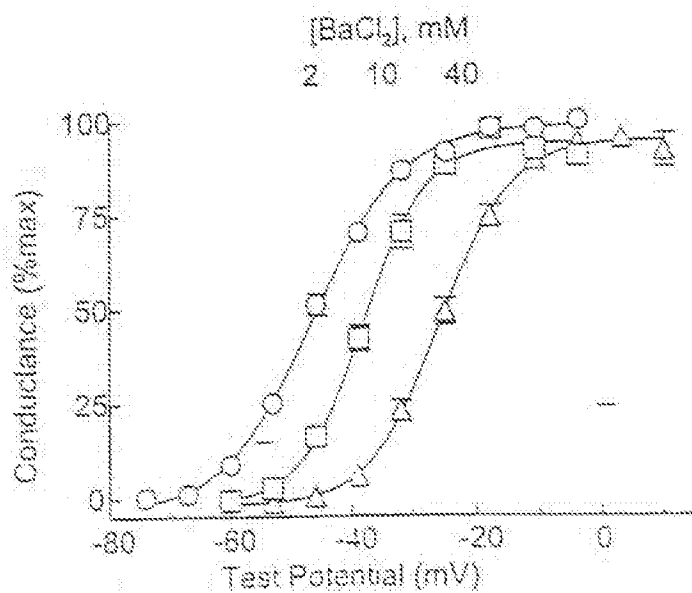


Figure 3B

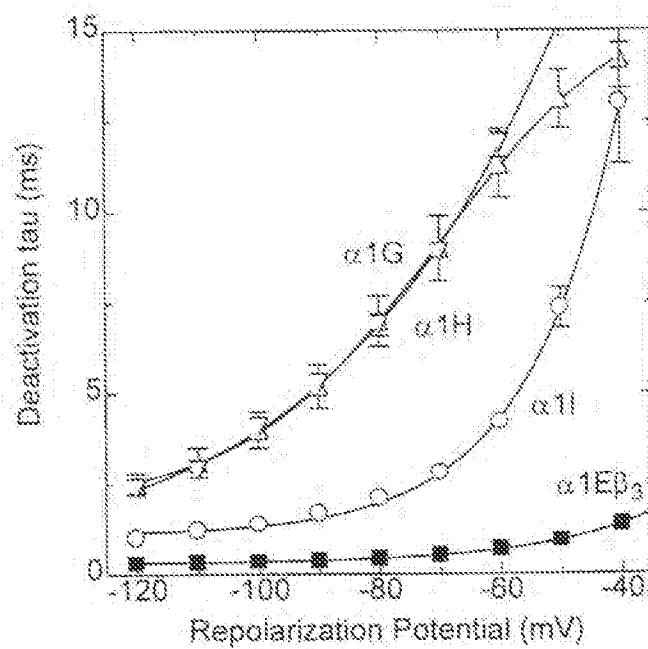
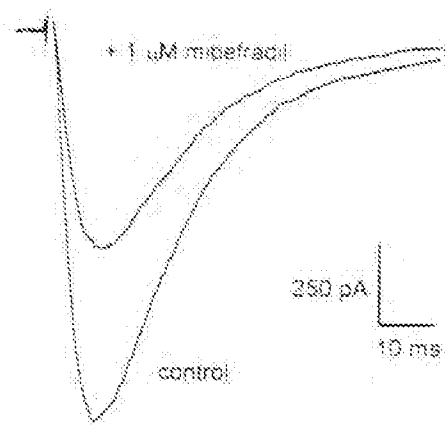
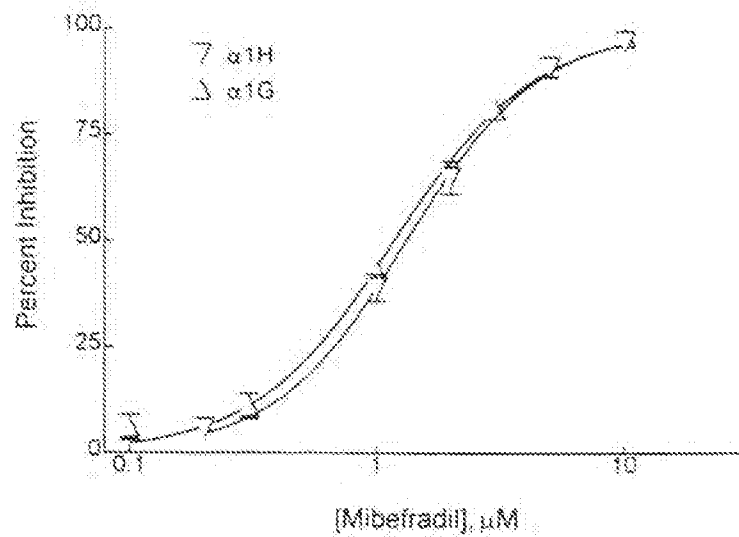


Figure 4

**Figure 5A****Figure 5B**

SEQUENCE LISTING

<110> Peter-Reyes, Edward
 Cribbs, Leanne L.
 Loyola University of Chicago

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 USING SAME

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 <151> 1997-12-05
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 Arg Ser Phe Met Arg Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Pro
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 Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Glu
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 Arg Cys Arg Ile Leu Glu Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe
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	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
				835			840						845				
65	ccg	gcg	ctg	cag	egg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
				850			855					860					
70	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	tcc	agg	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
				865		870				875					880		
75	atc	ctg	ggc	atg	cat	ctc	ttc	ggc	tgc	aag	ttt	gcc	tct	gag	cag	gat	2688
	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Gln	Arg	Asp	
				885				890						895			
80	ggg	gac	acc	ctg	cca	gac	egg	aag	aat	ttt	gac	tcc	ttg	ctc	tgg	gcc	2736

	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				900					905					910			
5	atc	gtc	act	gtc	ttt	cag	atc	ctg	acc	cag	gag	gac	tgg	aac	aaa	gtc	2784
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	Val	
				915				920					925				
10	ctc	tac	aat	ggt	atg	ggc	tcc	acg	tcc	tcc	tgg	gcg	gcc	ctc	tat	ttc	2832
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	Phe	
				930			935					940					
15	att	gac	ctc	atg	acc	ttc	ggc	aac	tac	gtg	ctc	ttc	aat	tgg	ctg	gtc	2880
	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
	945					950					955					960	
	gcc	att	ctg	gtg	gag	ggc	ttc	cag	gcg	gag	gga	gat	gcc	aac	aag	tcc	2928
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Lys	Ser	
					965				970						975		
20	gaa	tca	gag	ccc	gat	ttc	ttc	tca	ccc	agc	ctg	gat	ggt	gat	ggg	gac	2976
	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp	
				980					985					990			
25	agg	aag	aag	tgc	ttg	goc	ttg	gtg	tcc	ctg	gga	gag	cac	cag	gag	ctg	3024
	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu	
		995						1000					1005				
30	cgg	aag	agc	ctg	ctg	cag	ccc	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro	
	1010						1015					1020					
35	atg	tgg	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	ggg	ctg	ggc	3120
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly	
	1025					1030					1035				1040		
	ccc	ggg	tcc	cgc	cgc	acc	agc	agc	agc	ggg	tcc	gca	gag	ccc	ggg	ggg	3168
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala	
				1045						1050				1055			
40	gcc	cac	gag	atg	aag	tca	cgg	ccc	agc	gcc	cgc	agc	tct	ccg	cac	agc	3216
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser	
				1060				1065					1070				
45	ccc	tgg	agc	gct	gaa	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	ggg	aac	3264
	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	Arg	Asn	
		1075						1080				1085					
50	agc	ctc	ggc	cgt	gca	ccc	agc	ctg	aag	cgg	aga	agc	cca	agt	gga	gag	3312
	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu	
	1090					1095					1100						
55	cgg	ggg	tcc	ctg	ttg	tcc	ggc	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu	
	1105				1110					1115				1120			
	gag	agc	tca	gaa	gag	gag	cgg	gcc	agc	ccc	ggc	ggc	agt	gac	cat	cgc	3408
	Glu	Ser	Ser	Glu	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg	
				1125				1130					1135				
60	cac	agg	ggg	tcc	ctg	gag	cgg	gag	gcc	aag	agt	tcc	ttt	gac	ctg	cca	3456
	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	Leu	Pro	
				1140				1145					1150				
	gac	aca	ctg	cag	gtg	cca	ggg	ctg	cat	cgc	act	gac	agt	ggc	cga	ggg	3504

	Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly	
	1155 1160 1165	
5	tct gct tct gag cac cag gac tgc aat ggc aag tgg gct tca ggc cgc Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg	3552
	1170 1175 1180	
10	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Leu Asp Gly Asp Asp	3600
	1185 1190 1195 1200	
15	gcc gat gac gag gcc aac ctg agc aaa ggg gaa cgg gtc cgc gcg tgg Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp	3648
	1205 1210 1215	
	atc cga gcc cga ctc cct gcc tgc tgc ctc gag cga gac tcc tgg tca Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser	3696
	1220 1225 1230	
20	gcc tac atc ttc cct cgt sag taa agg ttc cgc ctc ctg tgt cac cgg Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg	3744
	1235 1240 1245	
25	atc atc acc cac aag atg ttc gac cac gtg gac ctt gtc atc atc ttc Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe	3792
	1250 1255 1260	
30	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His	3840
	1265 1270 1275 1280	
35	agc gct gaa cgc atc ttc ctg acc ctc tcc aat tac atc ttc acc gca Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala	3888
	1285 1290 1295	
	gac ttt ctg gct gaa atg aca ggg aag gtg gtg gca ctg gcc tgg tgc Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly Trp Cys	3936
	1300 1305 1310	
40	ttc ggg gag cag gcc tac ctg cgg agc agt tgg aac gtg ctg gac ggg Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu Asp Gly	3984
	1315 1320 1325	
45	ctg ttg gtg ctc atc tcc gtc atc gac att ctg gtg tcc atg gtc tct Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser	4032
	1330 1335 1340	
50	gac agc gcc acc aag atc ctg gcc atg ctg agg gtg ctg cgg ctg ctg Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu	4080
	1345 1350 1355 1360	
55	cgg acc ctg cgc cgg ctc agg gtg atc agc cgg gcg cag ggg ctg aag Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly Leu Lys	4128
	1365 1370 1375	
	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa gcc atc gcc aac att Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile	4176
	1380 1385 1390	
60	gta gtc atc tgc tgt gcc tuc ttc atc att ttc gcc atc ttg ggg gtg Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu Gly Val	4224
	1395 1400 1405	
	cag ctc ttc aaa ggg aag ttt ttc gtg tgc cag gcc gag gat acc agg	4272

	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Phe	Val	Cys	Gln	Gly	Glu	Asp	Thr	Arg	
	1410					1415					1420						
3	aaa	etc	acc	aac	aaa	tcc	gac	tgt	gac	gag	gcc	agt	tac	egg	tgg	gtc	4320
	Asn	Ile	Thr	Asn	Lys	Ser	Asp	Cys	Ala	Gln	Ala	Ser	Tyr	Arg	Trp	Val	
	1425				1430					1435					1440		
10	egg	cac	aag	tac	aac	ttt	gac	aac	ctt	ggc	cag	gcc	ctg	atg	tcc	ctg	4368
	Arg	His	Lys	Tyr	Asn	Phe	Asp	Asn	Leu	Gly	Gln	Ala	Leu	Met	Ser	Leu	
				1445					1450					1455			
15	ttc	gtt	tgg	gcc	tcc	aag	gat	ggt	tgg	gtg	gac	atc	atg	tac	gat	ggg	4416
	Phe	Val	Leu	Ala	Ser	Lys	Asp	Gly	Trp	Val	Asp	Ile	Met	Tyr	Asp	Gly	
			1460					1465					1470				
	ctg	gat	gct	gtg	ggc	gtg	gac	cag	cag	ccc	atc	arg	aac	cac	aac	ccc	4464
	Leu	Asp	Ala	Val	Gly	Val	Asp	Gln	Gln	Pro	Ile	Met	Asn	His	Asn	Pro	
		1475					1480					1485					
20	tgg	atg	ctg	ctg	tac	ttc	atc	tcc	ttc	ctg	ctc	att	gtg	gcc	ttc	ttt	4512
	Trp	Met	Leu	Leu	Tyr	Phe	Ile	Ser	Phe	Leu	Leu	Ile	Val	Ala	Phe	Phe	
	1490					1495						1500					
25	gtc	ctg	aac	atg	ttt	gtg	ggt	gtg	gtg	gtg	gag	aac	ttc	cac	aag	tgt	4560
	Val	Leu	Asn	Met	Phe	Val	Gly	Val	Val	Val	Gln	Asn	Phe	His	Lys	Cys	
	1505				1510					1515				1520			
30	egg	cag	cac	cag	gag	gaa	gag	gag	gcc	ggg	egg	egg	gag	gag	aag	ggc	4608
	Arg	Gln	His	Gln	Gln	Gln	Gln	Gln	Ala	Arg	Arg	Arg	Gln	Gln	Lys	Arg	
				1525					1530					1535			
35	cta	cga	aga	ctg	gag	aaa	aag	aga	agg	agt	aag	gag	aag	cag	atg	gct	4656
	Leu	Arg	Arg	Leu	Gln	Lys	Lys	Arg	Arg	Ser	Lys	Gln	Lys	Gln	Met	Ala	
			1540					1545					1550				
	gaa	gcc	cag	tgc	aaa	ccc	tac	tac	tcc	gac	tac	tcc	ggc	ttc	egg	etc	4704
	Glu	Ala	Gln	Cys	Lys	Pro	Tyr	Tyr	Ser	Asp	Tyr	Ser	Arg	Phe	Arg	Leu	
		1555				1560						1565					
40	ctc	gtc	cac	cac	tgg	tgc	acc	agg	cac	tac	ctg	gac	ctc	ttc	atc	aca	4752
	Leu	Val	His	His	Leu	Cys	Thr	Ser	His	Tyr	Leu	Asp	Leu	Phe	Ile	Thr	
	1570					1575						1580					
45	ggc	gtc	atc	ggg	ctg	aac	gtg	gtc	acc	atg	ggc	atg	gag	cac	tac	cag	4800
	Gly	Val	Ile	Gly	Leu	Asn	Val	Val	Thr	Met	Ala	Met	Gln	His	Tyr	Gln	
	1585				1590					1595					1600		
50	cag	ccc	cag	att	ctg	gat	gag	gct	ctg	aag	atc	tgc	aac	tac	atc	ttc	4848
	Gln	Pro	Gln	Ile	Leu	Asp	Glu	Ala	Leu	Lys	Ile	Cys	Asn	Tyr	Ile	Phe	
				1605					1610					1615			
55	act	gtc	atc	ttt	gtc	tgg	gag	tca	gtt	ttc	aaa	ctt	gtg	gcc	ttt	ggt	4896
	Thr	Val	Ile	Phe	Val	Leu	Gln	Ser	Val	Phe	Lys	Leu	Val	Ala	Phe	Gly	
			1620					1625					1630				
	ttc	cgt	egg	ttc	ttc	cag	gac	agg	tgg	aac	cag	ctg	gac	ctg	gcc	att	4944
	Phe	Arg	Arg	Phe	Phe	Gln	Asp	Arg	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Ile	
		1635					1640					1645					
60	gtg	ctg	ctg	tcc	atc	atg	ggc	etc	arg	ctg	gag	gaa	atc	gag	gtc	aac	4992
	Val	Leu	Leu	Ser	Ile	Met	Gly	Ile	Thr	Leu	Gln	Gln	Ile	Gly	Val	Asn	
	1650					1655						1660					
	gcc	tcc	ctg	ccc	atc	aac	ccc	acc	atc	atc	ggc	atc	atg	agg	gtg	ctg	5040

	Ala Ser Leu Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu	
	1665 1670 1675 1680	
5	cgc att gcc cga gtg ctg aag ctg ctg aag atg gct gtg ggc arg cgg Arg Ile Ala Arg Val Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg	5088
	1685 1690 1695	
10	ggg ctg ctg gac acg gtg atg cag gcc ctg ccc cag gtg ggg aac ctg Ala Leu Leu Asp Thr Val Met Gln Ala Leu Pro Gln Val Gly Asn Leu	5136
	1700 1705 1710	
15	gga ctt ctc ttc atg ttg ttg ttt ttc atc ttt gca gct ctg ggc gtg Gly Leu Leu Phe Met Leu Leu Phe Phe Ile Phe Ala Ala Leu Gly Val	5184
	1715 1720 1725	
20	gag ctg ttt gga gac ctg gag tgt gac gag aca cac ccc tgt gag ggc Glu Leu Phe Gly Asp Leu Glu Cys Asp Glu Thr His Pro Cys Glu Gly	5232
	1730 1735 1740	
25	ctg ggc cgt cat gcc acc ttt cgg aac ttt gcc atg gcc ttc cta acc Leu Gly Arg His Ala Thr Phe Arg Asn Phe Gly Met Ala Phe Leu Thr	5280
	1745 1750 1755 1760	
30	ctc ttc cga gtc tcc aca ggt gac aat tgg aat gcc att atg aag gac Leu Phe Arg Val Ser Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp	5328
	1765 1770 1775	
35	acc ctc cgg gac tgt gac cag gag tcc acc tgc tac aac acg gtc atc Thr Leu Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val Ile	5376
	1780 1785 1790	
40	tcg cct atc tac ttt gtg tcc ttc gtg ctg acg gcc cag ttc gtg cta Ser Pro Ile Tyr Phe Val Ser Phe Val Leu Thr Ala Gln Phe Val Leu	5424
	1795 1800 1805	
45	gtc aac gtg gtg atc gcc gtg ctg atg aag cac ctg gag gag agc aac Val Asn Val Val Ile Ala Val Leu Met Lys His Leu Glu Glu Ser Asn	5472
	1810 1815 1820	
50	aag gag gcc aag gag gag gcc gag cta gag gct gag ctg gag ctg gag Lys Glu Ala Lys Glu Glu Ala Glu Leu Glu Ala Glu Leu Glu Leu Glu	5520
	1825 1830 1835 1840	
55	atg aag acc ctc agc ccc cag ccc cag tcy cca ctg ggc agc ccc ttc Met Lys Thr Leu Ser Pro Gln Pro His Ser Pro Leu Gly Ser Pro Phe	5568
	1845 1850 1855	
60	ctc tgg cct ggg gtc gag gcc ccc gac agc ccc gac agc ccc aag cct Leu Trp Pro Gly Val Glu Gly Pro Asp Ser Pro Asp Ser Pro Lys Pro	5616
	1860 1865 1870	
65	ggg gct ctg cac cca ggg gcc cac ggg aga tca gcc tcc cac ttt tcc Gly Ala Leu His Pro Ala Ala His Ala Arg Ser Ala Ser His Phe Ser	5664
	1875 1880 1885	
70	ctg gag cac ccc acg atg cag ccc cag ccc acg gag ctg cca gga cca Leu Glu His Pro Thr Met Gln Pro His Pro Thr Glu Leu Pro Gly Pro	5712
	1890 1895 1900	
75	gac tta ctg aat gtg cgg aag tct ggg gtc agc cga acg cac tct ctg Asp Leu Leu Thr Val Arg Lys Ser Gly Val Ser Arg Thr His Ser Leu	5760
	1905 1910 1915 1920	
80	ccc aat gac agc tac atg tgt cgg cat ggg agc aat gcc gag ggg ccc	5808

	Pro	Asn	Asp	Ser	Tyr	Met	Cys	Arg	His	Gly	Ser	Thr	Ala	Glu	Gly	Pro	
					1925					1930						1935	
5	ctg	gga	caa	agg	ggc	tgg	ggg	ctc	ccc	aaa	ggt	cag	tca	ggc	tcc	gtc	5856
	Leu	Gly	His	Arg	Gly	Trp	Gly	Leu	Pro	Lys	Ala	Gln	Ser	Gly	Ser	Val	
				1940				1945						1950			
10	ttg	tcc	ggt	cac	tcc	cag	cca	gca	gat	acc	agg	tac	atc	ctg	cag	ctt	5904
	Leu	Ser	Val	His	Ser	Gln	Pro	Ala	Asp	Thr	Ser	Tyr	Ile	Leu	Gln	Leu	
				1955				1960						1965			
15	ccc	aaa	gah	gca	cct	cat	ctg	ctc	cag	ccc	cac	agg	gcc	cca	acc	tgg	5952
	Pro	Lys	Asp	Ala	Pro	His	Leu	Leu	Gln	Pro	His	Ser	Ala	Pro	Thr	Trp	
				1970				1975						1980			
20	ggc	acc	atc	ccc	aaa	ctg	ccc	cca	cca	gga	cgc	tcc	oct	ttg	ggt	cag	6000
	Gly	Thr	Ile	Pro	Lys	Leu	Pro	Pro	Pro	Gly	Arg	Ser	Pro	Leu	Ala	Gln	
				1985				1990						1995			2000
25	agg	cca	ctc	agg	cgc	cag	gca	gca	ata	agg	act	gac	tcc	ttg	gac	gtt	6048
	Arg	Pro	Leu	Arg	Arg	Gln	Ala	Ala	Ile	Arg	Thr	Asp	Ser	Leu	Asp	Val	
				2005					2010					2015			
30	cag	ggt	ctg	ggc	agg	cgg	gaa	gac	ctg	ctg	gca	gag	gtg	agt	ggg	ccc	6096
	Gln	Gly	Leu	Gly	Ser	Arg	Glu	Asp	Leu	Leu	Ala	Glu	Val	Ser	Gly	Pro	
				2020					2025					2030			
35	tcc	cgg	ccc	ctg	gcc	cgg	gcc	tac	tct	ttc	tgg	ggc	cag	tca	agt	acc	6144
	Ser	Pro	Pro	Leu	Ala	Arg	Ala	Tyr	Ser	Phe	Trp	Gly	Gln	Ser	Ser	Thr	
				2035				2040						2045			
40	cag	gca	cag	cag	cac	tcc	cgc	agg	cac	agg	aag	atc	tcc	aag	cac	atg	6192
	Gln	Ala	Gln	Gln	His	Ser	Arg	Ser	His	Ser	Lys	Ile	Ser	Lys	His	Met	
				2050				2055						2060			
45	acc	cgg	cca	gcn	cct	tgc	cca	ggc	cca	gaa	ccc	aac	tgg	ggc	aag	ggc	6240
	Thr	Pro	Pro	Ala	Pro	Cys	Pro	Gly	Pro	Gln	Pro	Asn	Trp	Gly	Lys	Gly	
				2065				2070						2075			2080
50	oct	cca	gag	ccc	aga	agg	agg	tta	gag	ttg	gac	acg	gag	ctg	agg	tgg	6288
	Pro	Pro	Glu	Thr	Arg	Ser	Ser	Leu	Glu	Leu	Asp	Thr	Glu	Leu	Ser	Trp	
				2085					2090					2095			
55	att	tca	gga	gac	ctc	ctg	ccc	cct	ggc	ggc	cag	gag	gag	ccc	cca	tcc	6336
	Ile	Ser	Gly	Asp	Leu	Leu	Pro	Pro	Gly	Gly	Gln	Glu	Glu	Pro	Pro	Ser	
				2100					2105					2110			
60	cca	cgg	gac	ctg	aag	aag	tgc	tac	agg	gtg	gag	gcc	cag	agg	tgc	cag	6384
	Pro	Arg	Asp	Leu	Lys	Lys	Cys	Tyr	Ser	Val	Glu	Ala	Gln	Ser	Cys	Gln	
				2115				2120						2125			
65	cgc	cgg	oct	acg	tcc	tgg	ctg	gat	gag	cag	agg	aga	caa	tct	atc	gcc	6432
	Arg	Arg	Pro	Thr	Ser	Trp	Leu	Asp	Glu	Gln	Arg	Arg	His	Ser	Ile	Ala	
				2130				2135						2140			
70	gtc	agg	tgc	ctg	gac	agg	ggc	tcc	caa	ccc	cac	ctg	ggc	aca	gac	ccc	6480
	Val	Ser	Cys	Leu	Asp	Ser	Gly	Ser	Gln	Pro	His	Leu	Gly	Thr	Asp	Pro	
				2145				2150						2155			2160
75	tct	aac	ctt	ggg	ggc	cag	cct	ctt	ggg	ggg	oct	ggg	agg	cgg	ccc	aag	6528
	Ser	Asn	Leu	Gly	Gly	Gln	Pro	Leu	Gly	Gly	Pro	Gly	Ser	Arg	Pro	Lys	
				2165					2170					2175			
80	aaa	aaa	ctc	agg	cgg	cct	agg	atc	ccc	ata	gac	ccc	ccc	gag	agg	caa	6576

	Lys	Lys	Leu	Ser	Pro	Pro	Ser	Ile	Thr	Ile	Asp	Pro	Pro	Gln	Ser	Gln	
			2180					2185						2190			
5	ggt	cct	agg	acc	ccg	ccc	agg	ccc	ggt	atc	tgc	ctc	agg	agg	agg	ggt	6624
	Gly	Pro	Arg	Thr	Pro	Pro	Ser	Pro	Gly	Ile	Cys	Leu	Arg	Arg	Arg	Ala	
			2195					2200					2205				
10	ccg	tcc	agg	gac	tcc	aag	gat	ccc	tig	gac	tct	ggc	ccc	cat	gac	agg	6672
	Pro	Ser	Ser	Asp	Ser	Lys	Asp	Pro	Leu	Ala	Ser	Gly	Pro	Pro	Asp	Ser	
			2210				2215					2220					
15	atg	gct	gac	tgc	ccc	tac	cca	aag	aaa	gat	gtg	ctg	agt	ctc	tcc	ggc	6720
	Met	Ala	Ala	Ser	Pro	Ser	Pro	Lys	Lys	Asp	Val	Leu	Ser	Leu	Ser	Gly	
			2225				2230				2235				2240		
	tta	tcc	tct	gac	cca	gca	gac	ctg	gac	ccc							6750
	Leu	Ser	Ser	Asp	Pro	Ala	Asp	Leu	Asp	Pro							
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	1				5				10					15			
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	Arg	Ser	Phe	Met	Arg	Leu	Asn	Asp	Leu	Ser	Gly	Ala	Gly	Gly	Arg	Pro	
			20					25					30				
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	Gly	Pro	Gly	Ser	Ala	Glu	Lys	Asp	Pro	Gly	Ser	Ala	Asp	Ser	Glu	Ala	
			35				40					45					
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	Glu	Gly	Leu	Pro	Tyr	Pro	Ala	Leu	Ala	Pro	Val	Val	Phe	Phe	Tyr	Leu	
		50					55				60						
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	Ser	Gln	Asp	Ser	Arg	Pro	Arg	Ser	Trp	Cys	Leu	Arg	Thr	Val	Cys	Asn	
	65				70				75				80				
	ccc	tgg	tct	gag	ggc	atc	agg	atg	tig	gtc	atc	ctt	ctc	aac	tgc	gtg	288
	Pro	Trp	Phe	Glu	Arg	Ile	Ser	Met	Leu	Val	Ile	Leu	Leu	Asn	Cys	Val	
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	Thr	Leu	Gly	Met	Phe	Arg	Pro	Cys	Gln	Asp	Ile	Ala	Cys	Asp	Ser	Gln	
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	Arg	Cys	Arg	Ile	Leu	Gln	Ala	Phe	Asp	Asp	Phe	Ile	Phe	Ala	Phe	Phe	
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	Ala	Val	Glu	Met	Val	Val	Lys	Met	Val	Ala	Leu	Gly	Ile	Phe	Gly	Lys	

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	Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala							
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	Arg Arg Leu Ala Glu Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu							
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	Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser							
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	cac cac cac cac cat cac cac cac tac cac ctg ggc aat ggg acg ctg	1536						
30	His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu							
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	agg gcc ccc cgg gcc agc cgg gag atc cag gag agg gat gcc aat ggg	1584						
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	Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp							
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	tgc cac tta gag cca gtc cgc tgc cag gcc cca cct ccc agg tcc cca	1728						
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	tct gag gca tcc gcc agc act gtg gcc agc ggg aag gtg tat ccc acc	1776						
	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr							
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	Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val							
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	Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile							
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	Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser							
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55	gag gcc gag cta gag gct gag ctg gag ctg gag atg aag acc ctc agc Gln Ala Glu Leu Glu Ala Gln Leu Glu Leu Glu Met Lys Thr Leu Ser 1845 1850 1855	5568			
60	ccc cag ccc cac tgg cca ctg gcc agc ccc ttc ctc tgg cct ggg gtc Pro Gln Pro His Ser Pro Leu Gly Ser Pro Phe Leu Trp Pro Gly Val 1860 1865 1870	5616			
65	gag gcc ccc gac agc ccc gac agc ccc aag cct ggg gct ctg cac cca Glu Gly Pro Asp Ser Pro Asp Ser Pro Lys Pro Gly Ala Leu His Pro 1875 1880 1885	5664			
70	ggg gcc cac ggg aga tca gcc tcc cac ttt tcc ctg gag cac cac acg Ala Ala His Ala Arg Ser Ala Ser His Phe Ser Leu Glu His Pro Thr 1890 1895 1900	5712			
75	atg cag ccc cac ccc acg gag ctg cca gga cca gac tta ctg act gtc Met Gln Pro His Pro Thr Glu Leu Pro Gly Pro Asp Leu Leu Thr Val 1905 1910 1915 1920	5760			
80	cgg aag tct ggg gtc agc cga acg cac tct ctg ccc aat gac agc tac Arg Lys Ser Gly Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr 1925 1930 1935 1940	5808			

	1925	1930	1935	
3	atg tgt cgg cat ggg agc act gca gag ggg ccc ctg gga cac agg ggc Met Cys Arg His Gly Ser Thr Ala Gln Gly Pro Leu Gly His Arg Gly 1940 1945 1950	5856		
10	tgg ggg ctg ccc aaa gct cag tca ggc tcc gtc ttg tcc gtt ccc tcc Trp Gly Leu Pro Lys Ala Gln Ser Gly Ser Val Leu Ser Val His Ser 1955 1960 1965	5904		
15	cag cca gca gat acc agc tac atc ctg cag ctt ccc aaa gat gca cct Gln Pro Ala Asp Thr Ser Tyr Ile Leu Gln Leu Pro Lys Asp Ala Pro 1970 1975 1980	5952		
20	cat ctg ctc cag ccc cac agc ggc cca aac tgg ggc acc atc ccc aaa His Leu Leu Gln Pro His Ser Ala Pro Thr Trp Gly Thr Ile Pro Lys 1985 1990 2000	6000		
25	ctg ccc cca ccc gga cgc tcc cct ttg gct cag agg cca ctg agg cgc Leu Pro Pro Pro Gly Arg Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg 2005 2010 2015	6048		
30	cag gca gca ata agg act gac tcc ttg gac gtt cag ggt ctg ggc agc Gln Ala Ala Ile Arg Thr Asp Ser Leu Asp Val Gln Gly Leu Gly Ser 2020 2025 2030	6096		
35	cgg gaa gac ctg ctg gaa gag gtg agt ggg ccc tcc cgg ccc ctg gcc Arg Glu Asp Leu Leu Ala Gln Val Ser Gly Pro Ser Pro Pro Leu Ala 2035 2040 2045	6144		
40	cgg gcc tac tct ttc tgg ggc cag tca agt acc cag gca cag cag cac Arg Ala Tyr Ser Phe Trp Gly Gln Ser Ser Thr Gln Ala Gln Gln His 2050 2055 2060	6192		
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50	tgc cca ggc cca gaa ccc aac tgg ggc aag ggc cct cca gag acc aga Cys Pro Gly Pro Gln Pro Asn Trp Gly Lys Gly Pro Pro Gln Thr Arg 2085 2090 2095	6288		
55	agg agc cta gag ttg gac acg gag ctg agc tgg atc tca gga gac ctg Ser Ser Leu Gln Leu Asp Thr Gln Leu Ser Trp Ile Ser Gly Asp Leu 2100 2105 2110	6336		
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70	tgg ctg gat gag cag agg aga cac tct atc gcc gtc agc tgc ctg gac Trp Leu Asp Gln Gln Arg Arg His Ser Ile Ala Val Ser Cys Leu Asp 2145 2150 2155 2160	6480		
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80	cag cct att ggg ggg cct ggg agc cgg ccc aag aaa aaa ctg agc cgg Gln Pro Leu Gly Gly Pro Gly Ser Arg Pro Lys Lys Lys Leu Ser Pro 2180 2185 2190	6576		

	2180	2190	2195	
5	ccg agt atc acc ata gac ccc ccc gag agc aca ggt cct cgg acc cgg Pro Ser Ile Thr Ile Asp Pro Pro Gln Ser Gln Gly Pro Arg Thr Pro	2195	2200	2205
10	ccc agc cct ggt atc tgc ctc cgg agc agc gac cgg tcc agc gac tcc Pro Ser Pro Gly Ile Cys Leu Arg Arg Arg Ala Pro Ser Ser Asp Ser	2210	2215	2220
15	aag gat ccc ttg gcc tat ggc ccc cct gac agc atg gct gcc tgg ccc Lys Asp Pro Leu Ala Ser Gly Pro Pro Asp Ser Met Ala Ala Ser Pro	2225	2230	2235
20	ccc cca aag aca gat gtg ctg agc ctc ccc ggt tta tcc cca gac cca Ser Pro Lys Lys Asp Val Leu Ser Leu Ser Gly Leu Ser Ser Asp Pro	2240	2245	2250
25	gca gac ctg gac acc Ala Asp Leu Asp Pro	2255	2260	2265
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50	ggg cgg ggg tca gca gaa aag gac cgg ggc agc gcc gag tcc gag ggg Gly Pro Gly Ser Ala Gln Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	35	40	45
55	gag ggg ctg cgg tac cgg gcc ctg gcc cgg gtg gtn ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	50	55	60
60	agc cag gac agc cgg cgg cgg agc tgg tgt ctc cgg acc ggc tgt aac Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn	65	70	75
65	ccc tgg ttc gag cgc atc agc atg ttg gtc atc ctt ctc aac tgc gtg Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val	80	85	90
70	acc ctg gcc atg ttc cgg cca tgc gag gac atc gcc tgt gac tcc cag Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	100	105	110
75	cgc tgc cgg atc ctg aag gcc ttt gat gac ttc atc ttt gcc ttc ttc Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe	115	120	125

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	Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys	
	130 135 140	
10	aag agc aac ctg gga gcc acc tgg aac cgg att gac ttc ttc acc gcc 480	
	Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val	
	145 150 155 160	
15	atc gca ggg atg cng gag tac tgg ctg gac ctg tag aac gcc acc ttc 528	
	Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Glu Asn Val Ser Phe	
	165 170 175	
20	tca ggt gtc agg aca gtc cgt ggg ctg cga cgg ctc agg gcc att aac 576	
	Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn	
	180 185 190	
25	cgg gtc ccc acc atg cgc atc att gtc aag tgg ctg ctg gat acc ctg 624	
	Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu	
	195 200 205	
30	ccc atg ctg ggc aac gtc ctg atg ctc tgc ttc ctc gtc ttc ttc atc 672	
	Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile	
	210 215 220	
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	Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg	
	225 230 235 240	
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	Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu	
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	275 280 285	
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	290 295 300	
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	Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr	
	305 310 315 320	
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	Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn	
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	Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser	
	355 360 365	
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	Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe	
	370 375 380	

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	Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Glc Phe Ser Glu	
	385 390 395 400	
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	Thr Lys Gln Arg Glu Ser Glc Leu Met Arg Glu Gln Arg Val Arg Phe	
	405 410 415	
15	ctg tcc aac gcc agc acc ctg ggt agc ttc acc gag cct ggc agc tgc	1296
	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glc Pro Gly Ser Cys	
	420 425 430	
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	Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	
	435 440 445	
25	cgc agg ctg ggt cag gtc tct cgg gcc gca ggt ggc cgg gtt ggg ctg	1392
	Arg Arg Leu Ala Glc Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu	
	450 455 460	
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	Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Gln Thr Glc Pro Ser Ser	
	465 470 475 480	
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	Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His	
	485 490 495	
40	cac cac cac cac cat cac cac cac tac cac ctg gcc aat ggg acc ctg	1536
	His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu	
	500 505 510	
45	agg gcc ccc cgg gcc agc ccg gag atc cag gac agg gat gcc aat ggg	1584
	Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly	
	515 520 525	
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	Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp	
	545 550 555 560	
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	Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro	
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65	tct gag gca tcc gcc agg act gtg gcc agc ggg aag gtg tat ccc acc	1776
	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr	
	580 585 590	
70	gtg cac acc agc cct cca ccg gag acc ctg aag gag aag gca cta gta	1824
	Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val	
	595 600 605	
75	gag gtg gct gca agc tat ggg ccc cca acc ctc acc agc ctc aac atc	1872
	Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile	
	610 615 620	
80	cca ccc ggg ccc tac agc tcc atg cac aag ctg ctg gag aac cag aat	1920
	Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Glu Ser	
	625 630 635 640	

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	Thr Gly Ala Cys Gln Ser Ser Cys Lys Ile Ser Ser Pro Cys Leu Lys	645 650 655
10	gcc gac agc ggc gcc tgc ggt cca gac agc tga ccc aac tgc gcc cgg	2016
	Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg	660 665 670
15	gcc ggc gca ggg gag gtg gag ctc gcc gac cgt gaa atg ccc gac cca	2064
	Ala Gly Ala Gly Glu Val Glu Leu Ala Asp Arg Glu Met Pro Asp Ser	675 680 685
20	gac agc gag gca gtc tat gag ctc aca cag gat gac cag cac agc gac	2112
	Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp	690 695 700
25	ctc cgg gac ccc cac agc cgg cgg caa cgg agc ctg gcc cca gat gna	2160
	Leu Arg Asp Pro His Ser Arg Arg Gln Arg Ser Leu Gly Pro Asp Ala	705 710 715 720
30	gag acc agc tct gtg ctg gcc ttc tgg agc cta atc tgc gac acc ttc	2208
	Glu Pro Ser Ser Val Leu Ala Phe Trp Arg Leu Ile Cys Asp Thr Phe	725 730 735
35	cga aag att gtg gac agc aag tac ttt gcc cgg gga atc atg atc gcc	2256
	Arg Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile Ala	740 745 750
40	atc ctg gtc aac aca ctc agc atg ggc atc gaa tac cac gag cag ccc	2304
	Ile Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln Pro	755 760 765
45	gag gag ctc acc aac gcc cta gaa atc agc aac atc gtc ctc acc agc	2352
	Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr Ser	770 775 780
50	ctc ttt gcc ctg gag atg ctg ctg aag ctg ctt gtg tac ggt ccc ttt	2400
	Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro Phe	785 790 795 800
55	ggc tac atc aag aat ccc tac aac atc ttc gat ggt gtc atc gtg gtc	2448
	Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val Val	805 810 815
60	atc agc gtg tgg gag atc gtg gcc cag cag ggg gcc gcc ctg tgg gtg	2496
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65	ctg cgg acc ttc cgc ctg arg cgt gtg ctg aag ctg gtg cgc ttc ctg	2544
	Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe Leu	835 840 845
70	ccg gcg ctg cag cgg cag ctg gtg gtg atc atg aag acc atg gac aac	2592
	Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp Asn	850 855 860
75	gtg gcc acc ttc tgc atg ctg ctt atg ctc ttc atc ttc acc ttc agc	2640
	Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser	865 870 875 880
80	atc ctg gcc atg cac ctc ttc gcc tgc aag ttc gcc tct gag cgg gat	2688
	Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg Asp	885 890 895

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	Ile Val Thr Val Phe Gln Ile Leu Thr Gln Gln Asp Trp Asn Lys Val	
	915 920 925	
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	930 935 940	
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	945 950 955 960	
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30	gaa tca gag ccc gat ttc ttc tca ccc agc ctg gat ggt gat ggg gac	2976
	Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Leu Asp Gly Asp Gly Asp	
	980 985 990	
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	Arg Lys Lys Cys Leu Ala Leu Val Ser Leu Gly Gln His Pro Glu Leu	
	995 1000 1005	
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	Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr Pro	
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	1125 1130 1135	
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	1140 1145 1150	

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	1170 1175 1180	
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	Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp	
	1185 1190 1195 1200	
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	Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser	
	1220 1225 1230	
30	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctg ctg tgt cac cgg	3744
	Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg	
	1235 1240 1245	
35	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc	3792
	Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe	
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	Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile	
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	Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu	
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	Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr Asp Gly	
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	Arg Leu Leu Val His His Leu Cys Thr Ser His Tyr Leu Asp Leu Phe	
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65	Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	192
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	85 90 95	
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	Glu Ser Ser Glu Glu Glu Arg Ala Ser Pro Ala Gly Ser Asp His Arg	
	1125 1130 1135	

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	His Arg Gly Ser Leu Gln Arg Gln Ala Lys Ser Ser Phe Asp Leu Pro	
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	Ala Asp Asp Gln Gly Asn Leu Ser Lys Gly Gln Arg Val Arg Ala Trp	
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	His Ala Arg Ser Ala Ser His Phe Ser Leu Glu His Pro Thr Met Gln	
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80	tto tac aac ttc atc tac ttc att ctt cnc atc atc gtc ggc tcc ttc Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe 370 375 380	1152		

	370		375		380																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
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	625		630		635		640	
3	acg gga gcc tgc cac agc tcc tgc aaa atc tcc agc ccc tgc tcc aag	1963						
	Thr Gly Ala Cys Glu Ser Ser Cys Lys Ile Ser Ser Pro Cys Ser Lys		643		650		655	
10	gca gac agt gga gcc tgc ggg ccc gac agt tgt ccc tac agt gcc cgg	2016						
	Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg		660		665		670	
15	aca gga gca gga gag cca gag tcc gct gac cac gcc atg cct gac tca	2064						
	Thr Gly Ala Gly Glu Pro Glu Ser Ala Asp His Val Met Pro Asp Ser		675		680		685	
20	gac agc gag gct gtg tat gag ttc acc cag gac gcc cag cac agt gac	2112						
	Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp		690		695		700	
25	ctc cgg gat ccc cac agc cgg cgg cga cag cgg agc ctg ggc cca gat	2160						
	Leu Arg Asp Pro His Ser Arg Arg Arg Gln Arg Ser Leu Gly Pro Asp		705		710		715	720
30	gca gag cct agt tcc gtg ctg gct ttc tgg agg ctg acc tgt gac aca	2208						
	Ala Glu Pro Ser Ser Val Leu Ala Phe Trp Arg Leu Ile Cys Asp Thr		723		730		735	
35	ttc cgg aag atc gta gat agc aaa tac ttt ggc cgg gga atc atg atc	2256						
	Phe Arg Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile		740		745		750	
40	gcc atc ctg gcc aat aca ctc agc atg ggc atc gag tac cac gag cag	2304						
	Ala Ile Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln		755		760		765	
45	ccc gag gag ctc acc aac gcc ctg gaa atc agc aac atc gtc ttc acc	2352						
	Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr		770		775		780	
50	agc ctc ttc gcc ttg gag atg ctg ctg aaa ctg crt gtc tac ggt ccc	2400						
	Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro		785		790		795	800
55	ttt ggc tac att aag aat ccc tac aac atc ttt gat ggt gtc att gtg	2448						
	Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val		805		810		815	
60	gtc atc agt ctg tgg gag att gtg ggc cag cag gga ggt ggc ctg tcc	2496						
	Val Ile Ser Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser		820		825		830	
65	gtg ctg cgg acc ttc cgc ctg atg cgg gtg ctg aag ctg gtc cgc ttc	2544						
	Val Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe		835		840		845	
70	ctg cgg gcc ctg cag cgc cag ctc gtg gtg ctc atg aag acc atg gac	2592						
	Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp		850		855		860	
75	aac gtg gcc acc ttc tgc atg ctc ctc atg ctg ttc atc ttc atc ttc	2640						
	Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe		865		870		875	880
80	agc arc cng gcc atg cat ctc ttc ggt tgc aag ctc gca tcc gaa cgg	2688						
	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg							

	885	890	895	
3	gat ggg gac atg ttg cca gac cgg aag aat ttc gac tcc atg ctc tgg Asp Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp 900 905 910	2736		
10	ggc atc gtc act gtc ttt cag att atg act cag gaa gac tgg aat aaa Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Gln Asp Trp Asn Lys 915 920 925	2784		
15	gtc ctc tac aac ggc atg gcc tcc acc tgg tot tgg gct gct ctt tac Val Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr 930 935 940	2832		
20	ttc atc gcc ctc atg act ttt ggc aac tac gtg ctc ttr aac ctg ctg Phe Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu 945 950 955 960	2880		
25	gtg gcc att ctt gtg gaa gga ttc cag gca gag gga gat gcc acc aag Val Ala Ile Leu Val Gln Gly Phe Gln Ala Gln Gly Asp Ala Thr Lys 965 970 975	2928		
30	tot gag tca gag act gat ttc ttr tgg ccc agt gtg gat ggt gat ggg Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Val Asp Gly Asp Gly 980 985 990	2976		
35	gac aga aag aag cgc ttg gcc ctg gtg gct ttg gga gaa cac gcg gaa Asp Arg Lys Lys Arg Leu Ala Leu Val Ala Leu Gly Glu His Ala Glu 995 1000 1005	3024		
40	cta cga aag agc ctt ttg cca ccc ctc atc atc cat acg gct gcg aca Leu Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr 1010 1015 1020	3072		
45	cca atg tca cac ccc aag agc tcc agc aca ggt gtg ggg gaa gca ctg Pro Met Ser His Pro Lys Ser Ser Ser Thr Gly Val Gly Glu Ala Leu 1025 1030 1035 1040	3120		
50	ggc tot ggc tot cga cgt acc agt agc agt ggg tcc gct gag cct gga Gly Ser Gly Ser Arg Arg Thr Ser Ser Ser Gly Ser Ala Glu Pro Gly 1045 1050 1055	3168		
55	gct gcc cac cat gag atg aaa tgt ccg cca agt gcc cgc agc tcc ccg Ala Ala His His Glu Met Lys Cys Pro Pro Ser Ala Arg Ser Ser Pro 1060 1065 1070	3216		
60	cac agt ccc tgg agt gcg gca agc agc tgg acc agc agg cgc tcc agc His Ser Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser 1075 1080 1085	3264		
65	agg aac agc ctg ggc cgg gcc ccc agc cta aag cgg agg agc ccg agc Arg Asn Ser Leu Gly Arg Ala Pro Ser Leu Lys Arg Arg Ser Pro Ser 1090 1095 1100	3312		
70	ggg gag cgg agg tcc ctg ctg tot gga gag gcc cag gag agt cag gat Gly Glu Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp 1105 1110 1115 1120	3360		
75	gag gag gaa agt tca gaa gag gac cgg gcc agc cca gca ggc agt gac Glu Glu Glu Ser Ser Glu Glu Asp Arg Ala Ser Pro Ala Gly Ser Asp 1125 1130 1135	3408		
80	cat cgc cac agg ggt tcc ttg gaa agt gag gcc aag agt tcc ttt gac His Arg His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp 1140 1145 1150	3456		

	1140	1145	1150	
5	cgg cct gac act ctg cag gtg ccg ggg ctg cac cgc acc gcc agc ggc Leu Pro Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly 1155 1160 1165	3504		
10	cgg agc tct gcc tct gag cac caa gac tgt aat gcc aag ccg gct tca Arg Ser Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser 1170 1175 1180	3552		
15	ggg cgt ttg gcc cgc acc ctg agg act gat gac ctc caa ctg gat ggg Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly 1185 1190 1195 1200	3600		
20	gat gat gac aat gat gag gga aat ctg agc aaa ggg gaa cgc ata caa Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Gln Arg Ile Gln 1205 1210 1215	3648		
25	gcc tgg gtc aga tcc cgg ctc cct gcc tgt tgc cga gag cga gat tcc Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Gln Arg Asp Ser 1220 1225 1230	3696		
30	tgg tgg gcc tar atc ttt cct cct cag tea agg ttt cgt ctc ctg tgt Trp Ser Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys 1235 1240 1245	3744		
35	cac cgg atc atc acc cac aag atg ttt gac cat gtg gtc ctc gtc atc His Arg Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile 1250 1255 1260	3792		
40	atc ttc ctc aac tgt atc acc atc ggt atg gag cgc ccc aaa att gac Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp 1265 1270 1275 1280	3840		
45	ccc cac agc gct gag cgc atc ttc ctg acc ctc tcc aac tac atc ttc Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe 1285 1290 1295	3888		
50	acg gca gtc ttt cta gct gaa atg aca gtg aag gtg gtc gca ctg ggc Thr Ala Val Phe Leu Ala Gln Met Thr Val Lys Val Val Ala Leu Gly 1300 1305 1310	3936		
55	tgg tgc ttt ggg gag cag gcc tac ctg cgc agc agc tgg aat gtg ctg Trp Cys Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu 1315 1320 1325	3984		
60	gac gcc ttg ctg gtg ctc atc tcc gtc atc gac atc ctg gtc tcc atg Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met 1330 1335 1340	4032		
65	gtc tcc gac agc gcc acc aag atc ctt gcc atg ctg agg gtg ctg cgg Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg 1345 1350 1355 1360	4080		
70	ctg ctg cgg acc ctg cgt cca ctc agg gtc atc agc cgg gcc cag gga Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly 1365 1370 1375	4128		
75	ctg aag ctg gtg gta gag act ctg atg tca tcc ctc aaa ccc att gcc Leu Lys Leu Val Val Gln Thr Leu Met Ser Ser Leu Lys Pro Ile Gly 1380 1385 1390	4176		
80	aac att gtg gtc att tgc tgt gcc ttc ttc atc att ttt ggc att ctc Asn Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu 1395 1400	4224		

	1395	1400	1405	
5	ggg ggg cag ctc ttc aaa ggg aag ttc ttc gtg tgt cag ggc gag gac Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp 1410 1415 1420	4272		
10	acc agg aac atc act aac aaa tcc gac tgc gct gag gcc agt tcc cga Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg 1425 1430 1435 1440	4320		
15	tgg gtc cgg cac aag tac aac ttt gac aac ctg ggc cag gct ctg atg Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met 1445 1450 1455	4368		
20	tcc ctg ttt gtg ctg gcc tcc aag gat ggt tgg gtc gac atc atg tat Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr 1460 1465 1470	4416		
25	gat ggg ctg gat gct gtc ggc gtg gat cag cag gcc atc atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485	4464		
30	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctg ctg atc gtg gcc Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala 1490 1495 1500	4512		
35	ttc ttt gtc ctg aac atg ttt gtg gcc gtg gtc gtc gag aac ttc cac Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His 1505 1510 1515 1520	4560		
40	aag tgc aga cag cac cag gag gag gag gag gcc agg cgg cgt gag gag Lys Cys Arg Gln His Gln Glu Glu Glu Glu Ala Arg Arg Arg Glu Glu 1525 1530 1535	4608		
45	aag cga cta cgg agg ctg gag aaa aag aga agg agt aag gag aag cag Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Ser Lys Glu Lys Gln 1540 1545 1550	4656		
50	atg gcc gaa gcc cag tgc aag ccc tac tac tct gac tac tcc aga ttc Met Ala Glu Ala Gln Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe 1555 1560 1565	4704		
55	cgg ctg ctt gtc cac cac ctg tgt acc agc cac tac ctg gac ctg ttc Arg Leu Leu Val His His Leu Cys Thr Ser His Tyr Leu Asp Leu Phe 1570 1575 1580	4752		
60	atc act ggt gtc atc ggg ctg aac gtg gtc act atg gcc atg gaa cat Ile Thr Gly Val Ile Gly Leu Asn Val Val Thr Met Ala Met Glu His 1585 1590 1595 1600	4800		
65	tac cag cag ccc cag atc ctg gac gag gct ctg aag atc tgc aat tcc Tyr Gln Gln Pro Gln Ile Leu Asp Glu Ala Leu Lys Ile Cys Asn Tyr 1605 1610 1615	4848		
70	atc ttt acc gtc atc ttt gtc ttt gag tca gtt ttc aaa ctt gtg gcc Ile Phe Thr Val Ile Phe Val Phe Glu Ser Val Phe Lys Leu Val Ala 1620 1625 1630	4896		
75	ttt gcc ttc cgc cgt ttc ttc cag gac agg tgg aac cag ctg gac ctg Phe Gly Phe Arg Arg Phe Phe Glu Asp Arg Trp Asn Gln Leu Asp Leu 1635 1640 1645	4944		
80	gct att gtg ctt ctg tcc atc atg gcc atc aca ctg gag gag att gag Ala Ile Val Leu Leu Ser Ile Met Gly Ile Thr Leu Glu Glu Ile Glu 1650 1655 1660	4992		

	1650	1655	1660	
5	gtc aat ctg tcc cag ccc att aac ccc acc atc atc cgt atc atg agg Val Asn Leu Ser Leu Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg 1665 1670 1675 1680	5040		
10	gtg ctc cgc att ggc cga gtt ctg aag ctg ttg aag atg gct gtg ggc Val Leu Arg Ile Ala Arg Val Leu Lys Leu Leu Lys Met Ala Val Gly 1685 1690 1695	5088		
15	atg cgg gca ctg ctg cac acg gtg atg cag gcc ctg ccc cag gtg ggg Met Arg Ala Leu Leu His Thr Val Met Gln Ala Leu Pro Gln Val Gly 1700 1705 1710	5136		
20	aac ctg gga ctt ctc ttc arg tta ctg ttt ttc atc ttt gaa gct ctg Asn Leu Gly Leu Leu Phe Met Leu Leu Phe Phe Ile Phe Ala Ala Leu 1715 1720 1725	5184		
25	ggc gtg gag ctc ttt gga gac ctg gag tgt gat gag aca cac cct tgt Gly Val Glu Leu Phe Gly Asp Leu Glu Cys Asp Gln Thr His Pro Cys 1730 1735 1740	5232		
30	gag gcc ttg ggt cgg cat gcc acc ttt agg aac ttt ggt atg gcc ttt Glu Gly Leu Gly Arg His Ala Thr Phe Arg Asn Phe Gly Met Ala Phe 1745 1750 1755 1760	5280		
35	ctg acc ctc ttc cga gtc tcc act ggt gac aac tgg aat ggt att atg Leu Thr Leu Phe Arg Val Ser Thr Gly Asp Asn Trp Asn Gly Ile Met 1765 1770 1775	5328		
40	aag gac acc ctc cgg gac tgt gac cag gag tcc acc tgc tac aac act Lys Asp Thr Leu Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr Asn Thr 1780 1785 1790	5376		
45	gtc atc tcc cct atc tac ttt gtg tcc ttc gtg ctg acg gcc cag ttt Val Ile Ser Pro Ile Tyr Phe Val Ser Phe Val Leu Thr Ala Gln Phe 1795 1800 1805	5424		
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55	agc aac aaa gag gcc aag gag gag gcc gag ctc gag gcc gag ctg gag Ser Asn Lys Glu Ala Lys Glu Glu Ala Glu Leu Glu Ala Glu Leu Glu 1825 1830 1835 1840	5520		
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65	ccc ttc ctc tgg ccc ggg gtg gag ggt gtc aac agt acg gac agc cct Pro Phe Leu Trp Pro Gly Val Glu Gly Val Asn Ser Thr Asp Ser Pro 1860 1865 1870	5616		
70	aag cct ggg gct cca cac acc act gcc cac att gga gca gcc tcc ggc Lys Pro Gly Ala Pro His Thr Thr Ala His Ile Gly Ala Ala Ser Gly 1875 1880 1885	5664		
75	ctc tcc ctt gag cac ccc acg atg gta ccc cac ccc gag gag gtg cca Phe Ser Leu Glu His Pro Thr Met Val Pro His Pro Glu Glu Val Pro 1890 1895 1900	5712		
80	gtc ccc cta gga ccc gac ctg ctg act gtg agg aag tct ggt gtc acc Val Pro Leu Gly Pro Asp Leu Leu Thr Val Arg Lys Ser Gly Val Ser 1905 1910 1915	5760		

	1905	1910	1915	1920	
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15	cag cca ggc tcc atc ttg ttc gtc cac tcc caa cca gca gac acc agc Gln Ser Gly Ser Ile Leu Ser Val His Ser Gln Pro Ala Asp Thr Ser 1955 1960 1965	5904			
20	tgc atc cta cag ctt ccc aaa gar gtg cac tat ctg ctg cag cct cac Cys Ile Leu Gln Leu Pro Lys Asp Val His Tyr Leu Leu Gln Pro His 1970 1975 1980	5952			
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65	gaa ccc ctg ttc cca cgg gac ctg aag aag tgc tac agt gta gag acc Glu Pro Leu Phe Pro Arg Asp Leu Lys Lys Cys Tyr Ser Val Glu Thr 2115 2120 2125	6384			
70	cag agc tgc agg cgc agg aat ggg ttc tgg cta gat gaa cag cgg aga Gln Ser Cys Arg Arg Arg Pro Gly Phe Trp Leu Asp Glu Gln Arg Arg 2130 2135 2140	6432			
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80	tgt cca agc ccc taa agc ctg ggg agc caa cct ctt ggg ggt cct ggc Cys Pro Ser Pro Ser Ser Leu Gly Gly Gln Pro Leu Gly Gly Pro Gly 2165 2170 2175 2180	6528			

	2165	2170	2175	
5	agg cgg cct aag aaa aaa ctc agc cca ccc agt atc tct ata gat ccc Ser Arg Pro Lys Lys Lys Leu Ser Pro Pro Ser Ile Ser Ile Asp Pro	2180	2185	2190
10	ccg gag agc cag ggc tct cgg cca cca tgg agt cct ggt gtc tgc ctc Pro Glu Ser Gln Gly Ser Arg Pro Pro Cys Ser Pro Gly Val Cys Leu	2195	2200	2205
15	agg agg agg ggg ccg gcc agt gac tct aag gat ccc tgg gtt tcc agc Arg Arg Arg Ala Pro Ala Ser Asp Ser Lys Asp Pro Ser Val Ser Ser	2210	2215	2220
20	ccc ctt gac agc acg gct gcc tca ccc tcc cca aag aaa gac acg ctg Pro Leu Asp Ser Thr Ala Ala Ser Pro Ser Pro Lys Lys Asp Thr Leu	2225	2230	2235
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50	ggg ccg ggg tgg acg gaa aag gac tgg ggc agc gcg gac tcc gag gcg Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	35	40	45
55	gag ggg atg ccg tcc ccg gcg ctc gcc ccg gtg gtt ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	50	55	60
60	agc cag gac agc cgc ccg ccg agc tgg tgt ctc cgc acg gtc tgt aac Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn	65	70	75
65	ccg tgg ttc gag cga gtc agt atg ctg gtc att ctt ctc aac tgt gtg Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val	80	85	90
70	act ctg ggt atg ttc agg ccg tgt gag gac att gcc tgt gac tcc cag Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	100	105	110
75	agg tgc cgg atc ctg cag gcc ttc gat gac ttc atc ttt gcc ttc ttt Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe	115	120	125

5	gct gtg gaa atg gtg gtg aag arg gtg gac ttg ggc atc ttt ggg aag	432
	Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys	
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	Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val	
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	Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe	
	165 170 175	
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	Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn	
	180 185 190	
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	Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu	
	195 200 205	
30	oct atg ctg ggc aac gtc ctg ctg ctg tgt ttc ttc gtc ttt ttc atc	672
	Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile	
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	Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg	
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	Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu	
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45	cct tat tac cag aca gag aat gag gac gag agc ccc ttc atc tgc tct	816
	Pro Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser	
	260 265 270	
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	Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu	
	275 280 285	
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	Arg Gly Glu Gly Gly Gly Gly Pro Pro Cys Ser Leu Asp Tyr Glu Thr	
	290 295 300	
60	tat aac agt tcc agc aac acc acc tgt gtc aac tgg aac cag tac tat	960
	Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr	
	305 310 315 320	
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	Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn	
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70	ttt gac aac att ggc tat gcc tgg atc gcc atc ttc cag gtc atc aca	1056
	Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr	
	340 345 350	
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	Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser	
	355 360 365	
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	Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe	
	370 375 380	

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	Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu	
	385 390 395 400	
10	acc aaa cag cgg gag agt cag ctg atg cgg gag cag cgt gta cga ttc	1248
	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe	
	405 410 415	
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	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys	
	420 425 430	
20	tat gag gag cta ctg aag tac ctg gtg tac atc ctg cga aaa gca gcc	1344
	Tyr Gln Gln Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	
	435 440 445	
25	cga agg ctg gcc cag gtc tct agg gct ata ggc gtg cgg gct ggg ctg	1392
	Arg Arg Leu Ala Gln Val Ser Arg Ala Ile Gly Val Arg Ala Gly Leu	
	450 455 460	
30	ctc agc agc cca gtg gcc cgt agt ggg cag gag ccc cag ccc agt ggc	1440
	Leu Ser Ser Pro Val Ala Arg Ser Gly Gln Glu Pro Gln Pro Ser Gly	
	465 470 475 480	
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	Ser Cys Thr Arg Ser His Arg Arg Leu Ser Val His His Leu Val His	
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	His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu	
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	Arg Val Pro Arg Ala Ser Pro Gln Ile Gln Asp Arg Asp Ala Asn Gly	
	515 520 525	
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	Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Thr Pro Ser Gly	
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	Cys His Leu Gln Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Cys Pro	
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	580 585 590	
70	gtg cat acc agc cct cca cca gag ata ctg aag gat aaa gca cta gtg	1824
	Val His Thr Ser Pro Pro Pro Glu Ile Leu Lys Asp Lys Ala Leu Val	
	595 600 605	
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	Gln Val Ala Pro Ser Pro Gly Pro Pro Thr Leu Thr Ser Phe Asn Ile	
	610 615 620	
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	Pro Pro Gly Pro Phe Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser	
	625 630 635 640	

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	Thr Gly Ala Cys His Ser Ser Cys Lys Ile Ser Ser Pro Cys Ser Lys	
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5	gca gac agt gga gcc tgc ggg ccg gac agt tgt ccc tac tgt gcc cgg	2016
	Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg	
	660 665 670	
10	aca gga gca gga gag cca gag tcc gct gac cat gtc atg cct gac tca	2064
	Thr Gly Ala Gly Glu Pro Glu Ser Ala Asp His Val Met Pro Asp Ser	
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	Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp	
	690 695 700	
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	705 710 715 720	
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	755 760 765	
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	785 790 795 800	
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	Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val	
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	820 825 830	
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	Val Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe	
	835 840 845	
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	Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp	
	850 855 860	
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	885 890 895	

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	915 920 926	
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	Arg Ser Ser Ala Ser Gln His Gln Asp Cys Asn Gly Lys Ser Ala Ser	
	1170 1175 1180	
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	Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly	
	1185 1190 1195 1200	
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	Asp Asp Asp Asn Asp Gln Gly Asn Leu Ser Lys Gly Gln Arg Ile Gln	
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	Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	

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	Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	
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	Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val	
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	Tyr	Glu	Glu	Leu	Leu	Lys	Tyr	Leu	Val	Tyr	Ile	Leu	Arg	Lys	Ala	Ala	
					435				440				445				
30	cga	agg	ctg	gac	cag	gtc	tct	agg	gct	ata	ggc	gtg	egg	gct	ggg	ctg	1392
	Arg	Arg	Leu	Ala	Gln	Val	Ser	Arg	Ala	Ile	Gly	Val	Arg	Ala	Gly	Leu	
	450						455					460					
35	ctc	agg	agc	cca	gtg	gcc	cgt	agt	ggg	cag	gag	ccc	cag	ccc	agt	ggc	1440
	Leu	Ser	Ser	Pro	Val	Ala	Arg	Ser	Gly	Gln	Glu	Pro	Gln	Pro	Ser	Gly	
	465					470					475					480	
40	agg	tgc	act	cgc	tca	cac	cgt	cgt	ctg	tct	gtc	cac	cac	ctg	gtc	cac	1488
	Ser	Cys	Thr	Arg	Ser	His	Arg	Arg	Leu	Ser	Val	His	His	Leu	Val	His	
					485					490					495		
45	cac	cat	cac	cac	cac	cat	cac	cac	tac	cac	ctg	ggt	aat	ggg	acg	ctc	1536
	His	His	His	His	His	His	His	His	Tyr	His	Leu	Gly	Asn	Gly	Thr	Leu	
					500				505					510			
50	aga	gtt	ccc	cgg	gcc	agc	cca	gag	atc	cag	gac	agg	gat	gcc	aat	ggg	1584
	Arg	Val	Pro	Arg	Ala	Ser	Pro	Glu	Ile	Gln	Asp	Arg	Asp	Ala	Asn	Gly	
					515				520				525				
55	tct	cgc	cgg	ctc	atg	cta	cca	cca	ccc	tct	aca	ccc	act	ccc	tct	ggg	1632
	Ser	Arg	Arg	Leu	Met	Leu	Pro	Pro	Pro	Ser	Thr	Pro	Thr	Pro	Ser	Gly	
		530					535					540					
60	ggc	cct	cgg	agg	ggt	gcg	gag	tct	gta	caa	agc	ttc	tac	cat	gct	gac	1680
	Gly	Pro	Pro	Arg	Gly	Ala	Gln	Ser	Val	His	Ser	Phe	Tyr	His	Ala	Asp	
	545					550				555						560	
65	tgc	cac	tgg	gag	cca	gtc	cgt	tgc	cag	gca	ccc	cct	ccc	agg	tgc	cca	1728
	Cys	His	Leu	Glu	Pro	Val	Arg	Cys	Gln	Ala	Pro	Pro	Pro	Arg	Cys	Pro	
					565					570					575		
70	tcg	gag	gca	tct	ggt	agg	act	gtg	ggt	agt	ggg	aag	gtg	tac	ccc	act	1776
	Ser	Gln	Ala	Ser	Gly	Arg	Thr	Val	Gly	Ser	Gly	Lys	Val	Tyr	Pro	Thr	
					580				585					590			
75	gtg	cat	acc	agg	cct	cca	cca	gag	ata	ctg	aag	gat	aaa	gca	cta	gtg	1824
	Val	His	Thr	Ser	Pro	Pro	Pro	Glu	Ile	Leu	Lys	Asp	Lys	Ala	Leu	Val	
					595			600					605				
80	gag	gtg	gac	ccc	agc	cct	ggg	ccc	ccc	acc	ctc	acc	agg	ttc	aac	atc	1872

	Glu	Val	Ala	Pro	Ser	Pro	Gly	Pro	Pro	Thr	Leu	Thr	Ser	Phe	Asn	Ile	
	610						615					620					
5	cca	ccg	ggg	ccc	ttc	agg	tcc	atg	cac	gag	ctc	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Phe	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
	625					630					635					640	
10	acg	gga	goc	tgc	cat	agg	tcc	tgc	aaa	atc	tcc	agg	ccg	tgc	tcc	gag	1968
	Thr	Gly	Ala	Cys	His	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Ser	Lys	
					645					650					655		
15	gta	gac	agt	gga	gcc	ggc	ggg	ccg	gac	agt	tgt	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660				665						670			
20	aca	gga	gca	gga	gag	cca	gag	tcc	gct	gac	cat	gtc	atg	ccg	gac	tca	2064
	Thr	Gly	Ala	Gly	Glu	Pro	Glu	Ser	Ala	Asp	His	Val	Met	Pro	Asp	Ser	
				675			680						685				
25	gac	agg	gag	gct	gtg	tac	gag	tcc	aca	cag	gac	gct	cag	cac	agt	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
				690			695					700					
30	ctc	cgg	gat	ccc	cac	agg	cgg	cgg	cga	cag	cgg	agg	ctg	ggc	cca	gat	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	
	705				710						715				720		
35	gca	gag	ccg	agt	tct	gtg	ctg	gct	tcc	tgg	agg	ctg	atc	tgt	gac	aca	2208
	Ala	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	
					725					730					735		
40	ttc	cgg	aag	atc	gta	gat	agg	aaa	tac	ttt	ggc	cgg	gga	atc	atg	atc	2256
	Phe	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	
				740					745					750			
45	gcc	atc	ctg	gtc	aat	aca	ctc	agg	atg	ggc	atc	gag	tac	cac	gag	cag	2304
	Ala	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	
				755				760					765				
50	ccc	gag	gag	ctc	acc	aac	gcc	ctg	gac	atc	agg	aac	atc	gtc	ttc	acc	2352
	Pro	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	
		770					775					780					
55	agg	ctc	tcc	gcc	ctg	gag	atg	ctg	ctg	aaa	ctg	ctt	gtc	tac	ggc	ccc	2400
	Ser	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	
					790					795					800		
60	ttt	ggc	tac	att	aag	aat	ccc	tac	aac	atc	ttt	gat	ggc	gtc	att	gtg	2448
	Phe	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	
					805					810					815		
65	gtc	atc	agt	gtg	tgg	gag	att	gtg	ggc	cag	cag	gga	ggt	ggc	ctg	tcc	2496
	Val	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	
				820					825					830			
70	gtg	ctg	cgg	acc	tcc	cgc	ctg	atg	cgg	gtg	ctg	aag	ctg	gtg	cgc	ttc	2544
	Val	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	
				835				840					845				
75	ctg	cgg	gcc	ctg	cag	cgc	cag	ctc	gtg	gtg	ctc	arg	aag	acc	atg	gac	2592
	Leu	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	
		850					855					860					
80	aac	gtg	ggc	acc	tcc	tgc	agg	ctc	ctc	atg	ctg	tcc	atc	tcc	atc	ctc	2640

	Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe	863	870	875	880
5	agg atc ctc ggc arg cat ctc ttt ggt tgc aag ctc gca tct gaa cgg	2688			
	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg	885	890	895	
10	gaa ggg gac acg ttg cca gac cgg aag aat ttc gac tcc ctc ctc tgg	2736			
	Asp Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp	900	905	910	
15	gac atc gtc act gtc ttt cag act ctc act cag gaa gac tgg aat aac	2784			
	Ala Ile Val Thr Val Phe Glu Ile Leu Thr Glu Glu Asp Trp Asn Lys	915	920	925	
20	gac ctc tcc aac ggc arg gcc tcc aca tcc tcc cgg gct gct ctt tcc	2832			
	Val Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr	930	935	940	
25	ttc atc gcc ctc atg act ttt ggc aac tat gtg ctc ttt aac ctc ctc	2880			
	Phe Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu	945	950	955	960
30	gtg gcc att ctt gtg gaa gga ttc cag gcc gag gga gat gcc acc aag	2928			
	Val Ala Ile Leu Val Glu Gly Phe Glu Ala Glu Gly Asp Ala Thr Lys	965	970	975	
35	tac gag tca gag cat gat ttc ttt tcc ccc agt gtg gat ggt gat ggg	2976			
	Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Val Asp Gly Asp Gly	980	985	990	
40	gac aga aag aag cgc atg gcc ctg gtg gct ttg gga gaa cac gcc gaa	3024			
	Asp Arg Lys Lys Arg Leu Ala Leu Val Ala Leu Gly Glu His Ala Glu	995	1000	1005	
45	cta cga aag agt ctt ttg cca ccc ctc atc atc cat aac gct gcc aca	3072			
	Leu Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr	1010	1015	1020	
50	cca atg tca cac ccc aag agc tcc agc aca ggt gtg ggg gaa gca ctg	3120			
	Pro Met Ser His Pro Lys Ser Ser Ser Thr Gly Val Gly Glu Ala Leu	1025	1030	1035	1040
55	ggc tct ggc tct cga cgt acc agt agc agt ggg tcc gct gag cat gga	3168			
	Gly Ser Gly Ser Arg Arg Thr Ser Ser Gly Ser Ala Glu Pro Gly	1045	1050	1055	
60	gct gcc cac cat gag atg aaa tgt ccg cca agt gcc cgg agc tcc ccg	3216			
	Ala Ala His His Glu Met Lys Cys Pro Pro Ser Ala Arg Ser Ser Pro	1060	1065	1070	
65	cac agt ccc tgg agt gcc gca agc agt tgg acc agc agg cgc tcc agc	3264			
	His Ser Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser	1075	1080	1085	
70	agg aac agc ctg ggc cgg gcc ccc agc cta aag cgg agg agc ccg agc	3312			
	Arg Asn Ser Leu Gly Arg Ala Pro Ser Leu Lys Arg Arg Ser Pro Ser	1090	1095	1100	
75	ggg gag cgg agg tcc ctg atg tct gga gag gcc cag gag agt cag gat	3360			
	Gly Glu Arg Arg Ser Leu Leu Ser Gly Glu Gly Glu Glu Ser Glu Asp	1105	1110	1115	1120
80	gag gag gaa agt tca gaa gag gac cgg gcc agc cca gca ggc agt gac	3408			

	Glu Glu Glu Ser Ser Glu Glu Asp Arg Ala Ser Pro Ala Gly Ser Asp	
	1125 1130 1135	
5	cat cgc cat agg ggt tcc ttg gaa cgt gag gcc aag agt tnc ttt gac His Arg His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp	3456
	1140 1145 1150	
10	ctg cct gac act ctg cag gtg ccg ggg ctg cac cgc acc gcc agc ggc Leu Pro Asp Thr Leu Glu Val Pro Gly Leu His Arg Thr Ala Ser Gly	3504
	1155 1160 1165	
15	egg agc tct gcc tct gag cac caa gac tgt aat ggc aag tcy gct tca Arg Ser Ser Ala Ser Glu His Glu Asp Cys Asn Gly Lys Ser Ala Ser	3552
	1170 1175 1180	
20	ggg cgt ttg gcc cgc acc ctg agg act gat gac ccc caa ctg gat ggg Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Glu Leu Asp Gly	3600
	1185 1190 1195 1200	
25	gat gat gac aat gat gag gga aat ctg agc aaa ggg gaa cgc ata caa Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Ile Glu	3648
	1205 1210 1215	
30	ggc tgg gtc aga tcc cgg ctt cct gcc tgt tgc cga gag cga gat tcc Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser	3696
	1220 1225 1230	
35	tgg tcy gcc tat atc ttt cct cct cag tca agg ttt cgt ctc ctg tgt Trp Ser Ala Tyr Ile Phe Pro Pro Glu Ser Arg Phe Arg Leu Leu Cys	3744
	1235 1240 1245	
40	cac cgg atc atc acc cac aag atg ttt gac cat gtg gtc ctc gtc atc His Arg Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile	3792
	1250 1255 1260	
45	atc ttc ctc aac tgt atc acc atc gct atg gag cgc ccc aaa att gac Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp	3840
	1265 1270 1275 1280	
50	ccc cac agc gct gag cgc atc ttc ctg acc ctc tcc aac tac atc ttc Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe	3888
	1285 1290 1295	
55	acg gca gtc ttt cta gct gaa atg aca gtg aag gtg gtg gca ctg ggc Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly	3936
	1300 1305 1310	
60	tgg tgc ttt ggg gag cag gcc tac ctg cgc agc agc tgg aat gtg ctg Trp Cys Phe Gly Glu Glu Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu	3984
	1315 1320 1325	
65	gac ggc ttg ctg gtg ctc atc tcc gtc atc gac atc ctg gtc tcc atg Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met	4032
	1330 1335 1340	
70	gtc tcc gac agc ggc acc aag atc ctt ggc atg ctg agg gtg ctg cgg Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg	4080
	1345 1350 1355 1360	
75	ctg ctg cgg acc ctg cgt cca ctc agg gtc atc agc cgg gcc cag gga Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Glu Gly	4128
	1365 1370 1375	
80	ctg aag ctg gtg gta gag act ctg atg tca tcc ctc aaa ccc att ggc	4176

	Leu	Lys	Leu	Val	Val	Gln	Thr	Leu	Met	Ser	Ser	Leu	Lys	Pro	Ile	Gly	
				1380					1385					1390			
5	aac	att	gag	gtc	att	tgc	tgt	gac	ctc	ttc	ata	att	ttt	gga	att	ctc	4224
	Asn	Ile	Val	Val	Ile	Cys	Cys	Ala	Phe	Phe	Ile	Ile	Phe	Gly	Ile	Leu	
			1395					1400					1405				
10	ggg	gtg	cag	ctc	ttc	aaa	ggg	aag	ctc	ttc	gtg	tgt	cag	ggt	gag	gac	4272
	Gly	Val	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Phe	Val	Cys	Gln	Gly	Glu	Asp	
		1410					1415					1420					
15	acc	agg	aac	ata	act	aac	aaa	taa	gac	tgc	gat	gag	gac	agg	tac	cga	4320
	Thr	Arg	Asn	Ile	Thr	Asn	Lys	Ser	Asp	Cys	Ala	Glu	Ala	Ser	Tyr	Arg	
	1425					1430					1435				1440		
20	tgg	gtc	cgg	cac	aag	tac	aac	ttt	gac	aac	ctg	ggc	cag	gct	ctg	atg	4368
	Trp	Val	Arg	His	Lys	Tyr	Asn	Phe	Asp	Asn	Leu	Gly	Gln	Ala	Leu	Met	
				1445					1450					1455			
25	tcc	ctg	ttt	gtg	ctg	gac	taa	aag	gat	ggt	tgg	gtt	gac	ata	atg	taa	4416
	Ser	Leu	Phe	Val	Leu	Ala	Ser	Lys	Asp	Gly	Trp	Val	Asp	Ile	Met	Tyr	
			1460					1465					1470				
30	gat	ggg	ctg	gat	gct	gtg	ggt	gtg	gat	cag	cag	ccc	ata	atg	aac	caa	4464
	Asp	Gly	Leu	Asp	Ala	Val	Gly	Val	Asp	Gln	Gln	Pro	Ile	Met	Asn	His	
		1475					1480					1485					
35	aac	ccc	tgg	atg	ctg	cca	tac	ttc	ata	ccc	ttc	ctc	ctc	ata	gtg	gcc	4512
	Asn	Pro	Trp	Met	Leu	Leu	Tyr	Phe	Ile	Ser	Phe	Leu	Leu	Ile	Val	Ala	
		1490					1495					1500					
40	ttc	ttt	gtc	ctg	aac	atg	ttt	gtg	ggc	gtg	gtg	gtg	gag	aac	ttc	cat	4560
	Phe	Phe	Val	Leu	Asn	Met	Phe	Val	Gly	Val	Val	Val	Gln	Asn	Phe	His	
	1505				1510					1515				1520			
45	aag	tgc	aga	cag	cac	cag	gag	gag	gag	gag	ggc	agg	cgg	cgt	gag	gag	4608
	Lys	Cys	Arg	Gln	His	Gln	Glu	Glu	Glu	Glu	Ala	Arg	Arg	Arg	Glu	Glu	
				1525				1530					1535				
50	aag	cga	cta	cgg	agg	ctg	gag	aaa	aag	aga	agg	aaa	gcc	cag	tgc	aag	4656
	Lys	Arg	Leu	Arg	Arg	Leu	Glu	Lys	Lys	Arg	Arg	Lys	Ala	Gln	Cys	Lys	
			1540					1545					1550				
55	ccc	tac	tac	tct	gac	tac	tgc	aga	ttc	ogg	ctc	ctt	gtc	caa	caa	ctg	4704
	Pro	Tyr	Tyr	Ser	Asp	Tyr	Ser	Arg	Phe	Arg	Leu	Leu	Val	His	His	Leu	
		1555					1560					1565					
60	tgt	acc	agc	cac	tac	ctg	gac	ctc	ttc	ata	act	ggt	gtc	ata	ggg	ctg	4752
	Cys	Thr	Ser	His	Tyr	Leu	Asp	Leu	Phe	Ile	Thr	Gly	Val	Ile	Gly	Leu	
		1570					1575				1580						
65	aac	gtg	gtc	act	atg	gcc	atg	gaa	cat	tac	cag	cag	ccc	cag	ata	ctg	4800
	Asn	Val	Val	Thr	Met	Ala	Met	Glu	His	Tyr	Gln	Gln	Pro	Gln	Ile	Leu	
	1585					1590					1595				1600		
70	gac	gag	gct	ctg	aag	ata	tgc	aat	tac	ata	ttt	acc	gtc	ata	ttt	gtc	4848
	Asp	Glu	Ala	Leu	Lys	Ile	Cys	Asn	Tyr	Ile	Phe	Thr	Val	Ile	Phe	Val	
				1605					1610					1615			
75	ttt	gag	tca	gtt	ttc	aaa	ctt	gtg	ggc	ttt	ggc	ttc	cgc	cgt	ttc	ata	4896
	Phe	Glu	Ser	Val	Phe	Lys	Leu	Val	Ala	Phe	Gly	Phe	Arg	Arg	Phe	Phe	
			1620				1625						1630				
80	cag	gac	agg	tgg	aac	cag	ctg	gac	ctg	gct	att	gtg	ctt	ctg	taa	ata	4944

	Gln Asp Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu Ser Ile	
	1635 1640 1643	
5	atg ggc atc acc ctg gag gag atc gag gtc aac ctg tcy ctg ccc atc Met Gly Ile Thr Leu Glu Gln Phe Glu Val Asn Leu Ser Leu Pro Ile	4992
	1650 1655 1660	
10	aac ccc acc atc atc cgt atc atg agc gtc ctc cgc acc gct cga gtt Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg Val	5040
	1665 1670 1675 1680	
15	ctg aag ctg ttg aag atg gct gtc ggc atg cgc gca ctg ctg cac acg Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg Ala Leu Leu His Thr	5088
	1685 1690 1695	
	ggc atg cag gcc ctg ccc cag gtc ggc aac ctg gga ctt ctc ttc atg Val Met Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe Met	5136
	1700 1705 1710	
20	tta ttg ttt ttc atc ttt gca gct ctg gcc gtc gag ctc ttt gga gac Leu Leu Phe Phe Ile Phe Ala Ala Leu Gly Val Glu Leu Phe Gly Asp	5184
	1715 1720 1725	
25	ctg gag tgt gat gag aca cac aat tgt gag gcc ttg ggt cgg aat gcc Leu Gln Cys Asp Glu Thr His Pro Cys Glu Gly Leu Gly Arg His Ala	5232
	1730 1735 1740	
30	acc ttt agg aac ttt ggt atg gcc ttt ctg acc ctc ttc cga gtc tcc Thr Phe Arg Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val Ser	5280
	1745 1750 1755 1760	
35	act ggt gac aac tgg aat ggt att atg aag gac acc ctc cgg gac tgt Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Asp Cys	5328
	1765 1770 1775	
	gac cag gag tcc acc tgc tac aac act gtc atc tcc cct atc tac ttt Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val Ile Ser Pro Ile Tyr Phe	5376
	1780 1785 1790	
40	gtg tcc ttc gtg ctg aag gcc cag ttt gtg ctg gtc aac gtg gtc ata Val Ser Phe Val Leu Thr Ala Gln Phe Val Leu Val Asn Val Val Ile	5424
	1795 1800 1805	
45	gct gtg ctg atg aag cac ctg gaa gaa agc aac aaa gag gcc aag gag Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys Glu Ala Lys Glu	5472
	1810 1815 1820	
50	gag gcc gag ctc gag gcc gag ctg gag ctg gag atg aag acg ctc agc Glu Ala Glu Leu Glu Ala Glu Leu Glu Leu Met Lys Thr Leu Ser	5520
	1825 1830 1835 1840	
55	cag cag ccc cac tcc ccg ctg ggc agc ccc ttc ctc tgg ccc ggg gtc Pro Gln Pro His Ser Pro Leu Gly Ser Pro Phe Leu Trp Pro Gly Val	5568
	1845 1850 1855	
	gag ggt gtc aac agt act gac agc cct aag cct ggg gcc cca cac acc Glu Gly Val Asn Ser Thr Asp Ser Pro Lys Pro Gly Ala Pro His Thr	5616
	1860 1865 1870	
60	act gcc cac att gga gca gcc tgc ggc ttc tcc ctt gag cac ccc acg Thr Ala His Ile Gly Ala Ala Ser Gly Phe Ser Leu Glu His Pro Thr	5664
	1875 1880 1885	
	atg gta ccc cac ccc gag gag gtc cca gtc ccc ctc gga cca gag atg	5712

	Met	Val	Pro	His	Pro	Glu	Glu	Val	Pro	Val	Pro	Leu	Gly	Pro	Asp	Leu	
	1890					1895						1900					
5	ctg	acc	gtg	agg	aag	tat	ggt	gtc	agg	cgg	acg	cac	tct	ctg	ccc	aac	5760
	Leu	Thr	Val	Arg	Lys	Ser	Gly	Val	Ser	Arg	Thr	His	Ser	Leu	Pro	Asn	
	1905				1910					1915					1920		
10	gac	agg	tac	atg	tgc	cgc	aac	ggg	agg	act	gct	gag	aga	tcc	cta	gga	5808
	Asp	Ser	Tyr	Met	Cys	Arg	Asn	Gly	Ser	Thr	Ala	Glu	Arg	Ser	Leu	Gly	
				1925					1930					1935			
15	cac	agg	ggc	tgg	ggg	ctc	ccc	aaa	gac	cag	tca	ggc	tcc	atc	ttg	tcc	5856
	His	Arg	Gly	Trp	Gly	Leu	Pro	Lys	Ala	Gln	Ser	Gly	Ser	Ile	Leu	Ser	
			1940					1945					1950				
	gtt	cac	tcc	caa	cca	gca	gac	acc	agg	tgc	atc	cra	cag	ctt	ccc	aaa	5904
	Val	His	Ser	Gln	Pro	Ala	Asp	Thr	Ser	Cys	Ile	Leu	Gln	Leu	Pro	Lys	
	1955						1960					1965					
20	gac	gtg	cac	tat	ctg	ctc	cag	ccr	cat	ggg	gct	ccc	acc	tgg	ggc	gcc	5952
	Asp	Val	His	Tyr	Leu	Leu	Gln	Pro	His	Gly	Ala	Pro	Thr	Trp	Gly	Ala	
	1970					1975						1980					
25	acc	ccc	aaa	cta	ccc	caa	ccr	ggc	cgc	tcc	ccc	ctg	gct	cag	agg	ccc	6000
	Ile	Pro	Lys	Leu	Pro	Pro	Pro	Gly	Arg	Ser	Pro	Leu	Ala	Gln	Arg	Pro	
	1985				1990					1995					2000		
30	ctc	agg	cgc	cag	gca	gca	ata	agg	act	gac	tcc	ctg	gat	gtg	cag	ggc	6048
	Leu	Arg	Arg	Gln	Ala	Ala	Ile	Arg	Thr	Asp	Ser	Leu	Asp	Val	Gln	Gly	
				2005						2010					2015		
35	ctg	ggt	agg	cgg	gaa	gac	ctg	ctg	tca	gag	gtg	agt	ggg	ccc	tcc	tgc	6096
	Leu	Gly	Ser	Arg	Glu	Asp	Leu	Leu	Ser	Glu	Val	Ser	Gly	Pro	Ser	Cys	
				2020					2025					2030			
	ccc	ctg	acc	cgg	tcc	tca	tcc	ttc	tgg	ggc	ggg	tcc	agg	atc	cag	gtg	6144
	Pro	Leu	Thr	Arg	Ser	Ser	Ser	Phe	Trp	Gly	Gly	Ser	Ser	Ile	Gln	Val	
		2035						2040					2045				
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	Gln	Gln	Arg	Ser	Gly	Ile	Gln	Ser	Lys	Val	Ser	Lys	His	Ile	Arg	Leu	
	2050					2055						2060					
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	Pro	Ala	Pro	Cys	Pro	Gly	Leu	Glu	Pro	Ser	Trp	Ala	Lys	Asp	Pro	Pro	
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	Gly	Asp	Leu	Leu	Pro	Ser	Ser	Gln	Glu	Glu	Pro	Leu	Phe	Pro	Arg	Asp	
			2100						2105				2110				
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	Leu	Lys	Lys	Cys	Tyr	Ser	Val	Glu	Thr	Gln	Ser	Cys	Arg	Arg	Arg	Pro	
		2115					2120					2125					
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	Gly	Phe	Trp	Leu	Asp	Glu	Gln	Arg	Arg	His	Ser	Ile	Ala	Val	Ser	Cys	
	2130					2135					2140						
	ctg	gac	agg	ggc	tcc	caa	ccc	cgc	cta	tgt	cca	agg	ccc	tca	agg	ctc	6480

	Leu Asp Ser Gly Ser Gln Pro Arg Leu Cys Pro Ser Pro Ser Ser Leu	
	2145 2150 2155 2160	
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	2165 2170 2175	
10	agc cca ccc agt atc tct ata gac aac ccg gag agc cag ggc tct cgg Ser Pro Pro Ser Ile Ser Ile Asp Pro Pro Glu Ser Gln Gly Ser Arg	6576
	2180 2185 2190	
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	2195 2200 2205	
	gac tct aag gat ccc tgg gtc tcc agc cca ctt gac agc aag gct gcc Asp Ser Lys Asp Pro Ser Val Ser Ser Pro Leu Asp Ser Thr Ala Ala	6672
	2210 2215 2220	
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	1 5 10 15	
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	20 25 30	
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	35 40 45	
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	50 55 60	
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	65 70 75 80	
	tgc ctc ggt cag acc acg ccg ccg cgc agc tgg tgc ctc cgg ctg gtc Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu Val	288
	85 90 95	
	tgc aac cca tgg ttc gag cag gtc agc atg ctg gta atc atg ctc aac Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu Asn	336

	100	105	110	
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15	ttt ttt gcg gtg gag atg gac atc aag atg gtg gcc ttc ggg ctg ttc Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu Phe 145 150 155 160	480		
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35	atc aac cgc gtg cct agc atg cgg atc ctg gtc act ctg ctg ctg gat Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp 210 215 220	672		
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	385	360	365	
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	610	615	620	
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	1125	1130	1135	
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	1890	1895	1900	
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	Cys Leu Gly Gln Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu Val	
	85 90 95	
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	Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu Asn	
	100 105 110	
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	Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys Gly	
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	Ala Ile Phe Gln Val Ile Thr Leu Gln Gly Trp Val Asp Ile Met Tyr	
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	Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile Leu	
	385 390 395 400	
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	Leu Ile Ile Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val	
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	Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Ser Gln Leu Met	
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	Arg His Arg Gly His Gly Pro Leu Ser Leu Asn Ser Pro Asp Pro Tyr	
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	Gly Phe Arg Arg Phe Phe Lys Asp Arg Trp Asn Glu Leu Asp Leu Ala	
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	Ala Glu Pro Gly Val Thr Thr Glu Gln Pro Gly Pro Arg Ser Pro Pro	
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	Ser Ser Pro Pro Gly Leu Glu Glu Pro Leu Asp Gly Ala Asp Pro His	
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10	gtc cca cac cca gac ctg gpg cct att gcc ttc ttc tgc ctg cga cag	192
	Val Pro His Pro Asp Leu Ala Pro Ile Ala Phe Phe Cys Leu Arg Gln	
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	Thr Thr Ser Pro Arg Asn Trp Cys Ile Lys Met Val Cys Asn Pro Trp	
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	Phe Glu Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr Leu	
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25	ggc atg tac cag ccg tgc gac gac atg gac tgc ctg tcc gac cgc tgc	336
	Gly Met Tyr Gln Pro Cys Asp Asp Met Asp Cys Leu Ser Asp Arg Cys	
	100 105 110	
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	Lys Ile Met Gln Val Phe Asp Phe Ile Phe Ile Phe Phe Ala Met	
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	Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Met Ala	
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45	ggg atg gtc gag tac tcc ctg gac ctt cag aac atc aac ctg tca gcc	528
	Gly Met Val Glu Tyr Ser Leu Asp Leu Gln Asn Ile Asn Leu Ser Ala	
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	Ile Arg Thr Val Arg Val Leu Arg Pro Leu Lys Ala Ile Asn Arg Val	
	180 185 190	
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	Pro Ser Met Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met	
	195 200 205	
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	Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile Phe Gly	
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	Tyr Gln Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Ser	
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	Gly Asp Asn Gly Ile Met Gly Cys His Gln Ile Pro Pro Leu Lys Glu	
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	Gln Gly Arg Gln Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly	
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15	cgt tac tac aat gtg tgc cgc acg ggc agc gcc aac ccc cac aag ggt	1008
	Arg Tyr Tyr Asn Val Cys Arg Thr Gly Ser Ala Asn Pro His Lys Gly	
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	Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln	
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	Val Ile Thr Leu Gln Gly Trp Val Gln Ile Met Tyr Tyr Val Met Asp	
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	Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln	
	385 390 395 400	
35	ttc tgg gag acc aag caa cgg gag cac cgg ctg atg ctg gag cag cgg	1248
	Phe Ser Gln Thr Lys Gln Arg Gln His Arg Leu Met Leu Gln Gln Arg	
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	Gln Arg Tyr Leu Ser Ser Ser Thr Val Ala Ser Tyr Ala Gln Pro Gly	
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	Asp Cys Tyr Gln Gln Ile Phe Gln Tyr Val Cys His Ile Leu Arg Lys	
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	Ala Lys Arg Arg Ala Leu Gly Leu Tyr Gln Ala Leu Gln Ser Arg Arg	
	450 455 460	
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	Gln Ala Leu Gly Pro Gln Ala Pro Ala Pro Ala Lys Pro Gly Pro His	
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	Ser Asp Pro Ala Ser Cys Pro Cys Cys Gln His Gln Asp Gly Arg Arg	
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	Gly Ser Ser Ala Gly Gly Glu Asp Glu Ala Asp Gly Asp Gly Ala Arg	
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	Ser Ser Glu Asp Gly Ala Ser Ser Glu Leu Gly Lys Glu Glu Glu Glu	
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	Glu Thr Arg Ala Lys Leu Arg Gly Ile Val Asp Ser Lys Tyr Phe Asn	
	595 600 605	
25	cgg ggc atc atg atg gcc atc ctg gtc aac acc gtc agc atg ggc atc	1872
	Arg Gly Ile Met Met Ala Ile Leu Val Asn Thr Val Ser Met Gly Ile	
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	Gln Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu Asp Gln Ser Ser Ser	
	835 840 845	
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	cta cgc agc agc tgg aac gtg ctg gat gcc ttt ctt gtc ttc gtg tcc	3648
	Leu Arg Ser Ser Trp Asn Val Leu Asp Gly Phe Leu Val Phe Val Ser	
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	Glu Pro Gly Ile Thr Glu Glu Pro Gly Pro Arg Ser Pro Pro Pro Ser	
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 Lys Met Ala
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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/23161

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/705 C07K16/28 C12N5/10 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 04144 A (NEUREX CORP) 9 February 1995	1,2,7, 10-18, 20-22
Y	see abstract; claims 1-10	3,19
X	NOONEY JM (REPRINT) ET AL: "Identifying neuronal non-L Ca2+ channels - more than stamp collecting?" TRENDS IN PHARMACOLOGICAL SCIENCES, 10-1997, 18, 363-371, XP002093637 see page 369, right-hand column - page 370, right-hand column	1,2, 10-16, 20-22

-/-

<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/> Patent family members are listed in annex.
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" documents published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p>	
Date of the actual completion of the international search <p style="text-align: center;">16 February 1999</p>	Date of making of the international search report <p style="text-align: center;">09/03/1999</p>
Name and mailing address of the ISA European Patent Office, P.O. Box 5518 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 551 epo nl, Fax: (+31-70) 340-3016	Authorized officer <p style="text-align: center;">Gurdjian, D</p>

INTERNATIONAL SEARCH REPORT

Internat'l Application No.

PCT/US 98/23161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ERTEL S I ET AL: "Low-voltage-activated T-type Ca ²⁺ channels" TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 18, no. 2, February 1997, page 37-42 XP004055849 see page 39, left-hand column, paragraph 4 - page 40, middle column, paragraph 1; table 1	1,2, 10-16, 20-22
X	DZHURA IO ET AL: "Characterization of hypothalamic low-voltage-activated Ca channels based on their functional expression in Xenopus oocytes." NEUROSCIENCE, FEB 1996, 70 (3) P729-38, XP002093638 UNITED STATES see the whole document	1,2, 10-18, 20-22
Y	WILSON R ET AL: "2.2 MB OF CONTIGUOUS NUCLEOTIDE SEQUENCE FROM CHROMOSOME III OF C. ELEGANS" NATURE, vol. 368, 3 March 1994, pages 32-38, XP002910426 see abstract	3,19
Y	& EMBL DATABASE Accession number g18840 WILSON R. ET AL. 1996 see the whole document	3,19
A	WO 93 04083 A (SALK INST BIOTECH IND) 4 March 1993 see abstract; claims 1-39	1-22
P,X	PEREZ-REYES E ET AL: "Molecular characterization of a neuronal low-voltage-activated T-type calcium channel 'see comments!'" NATURE, FEB 26 1998, 391 (6670) P896-900, XP002093639 ENGLAND see the whole document	1-15, 20-22
P,X	CRIBBS LL ET AL: "Cloning and characterization of alpha1H from human heart, a member of the T-type Ca ²⁺ channel gene family." CIRC RES, JUL 13 1998, 83 (1) P103-9, XP002093640 UNITED STATES see the whole document	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

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